DEAROMATIVE REDUCTION OF ARENES THROUGH THE USE OF ARENOPHILES
&
STUDIES TOWARDS THE SYNTHESIS OF CARDIOTONIC STEROIDS CALOTROPIN AND CALACTIN

BY

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THESIS

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ABSTRACT

A novel method for the dearomative reduction of arenes through the use of N,N-arenophile, MTAD, was developed. Cheap feedstock arenes undergo photocycloaddition with MTAD, and the cycloadduct can be treated further to furnish novel 1,3-cyclohexadienes or 1,4-diamino-2-cyclohexenes. The utility of this method is shown in the synthesis of a natural product in two steps from naphthalene.

Calotropin, a cardiotonic steroid, isolated from Apocynaceae plants is a highly cytotoxic natural product with anti-cancer activity. A total synthesis strategy which utilizes a NHC-catalyzed benzoin condensation, and Pd-catalyzed nucleophilic dearomatization of a phenol is described. Also described, is the semisynthetic strategy towards calotropin from estrone, where the aromatic A ring is dearomatized to introduce a C1 fragment at the *para*-position.

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ABBREVIATIONS

Bn – benzyl

DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene

DIBAL-H – diisobutylaluminum hydride

DMF – N,N-dimethylformamide

MTAD - 4-methyl-1,2,4-triazole-3,5-dione

NHC – N-heterocyclic carbene

Pd/C – palladium on carbon

PG – protecting group

Rf – retention factor

TBS – tertbutyldimethylsilyl

THF – tetrahydrofuran

THP – tetrahydropyran

TLC – thin layer chromatography

CHAPTER 1: DEAROMATIVE REDUCTION OF ARENES THROUGH THE USE OF ARENOPHILES

1.1. INTRODUCTION

Aromatic compounds such as benzene, toluene, and naphthalene are inexpensive, feedstock chemicals. These arenes can be converted into highly reactive dienes, and further manipulated to generate compounds of high molecular complexity. Examples of dearomatization reactions include: the Birch reduction, oxidative dearomatization of phenols, microbial arene oxidation, and stoichiometric transition metal-mediated transformations of arenes.[1,2] Such reactions are extremely powerful synthetic tools that have been used on industrial scales to synthesize pharmaceutical compounds; however, these methods are limited- in both the functionality that can be incorporated during the dearomatization step and the scope of compatible substrates.

Our research group has developed a novel approach for the dearomatization of arenes, which is based upon the *para*-photocycloaddition of an arenophile, 4-methyl-1,2,4-triazole-3,5-dione (MTAD) **1**, with an arene under visible light, to afford a cycloadduct **2** with two isolated olefins (Figure 1). [3] This cycloadduct can then undergo diimide reduction[4] on the less substituted olefin, furnishing reduced cycloadduct **3** which can be further manipulated to give cycloreverted product, cyclohexadiene **4**, or *N-N* bond cleaved product, diaminocyclohexene **5**.[5]

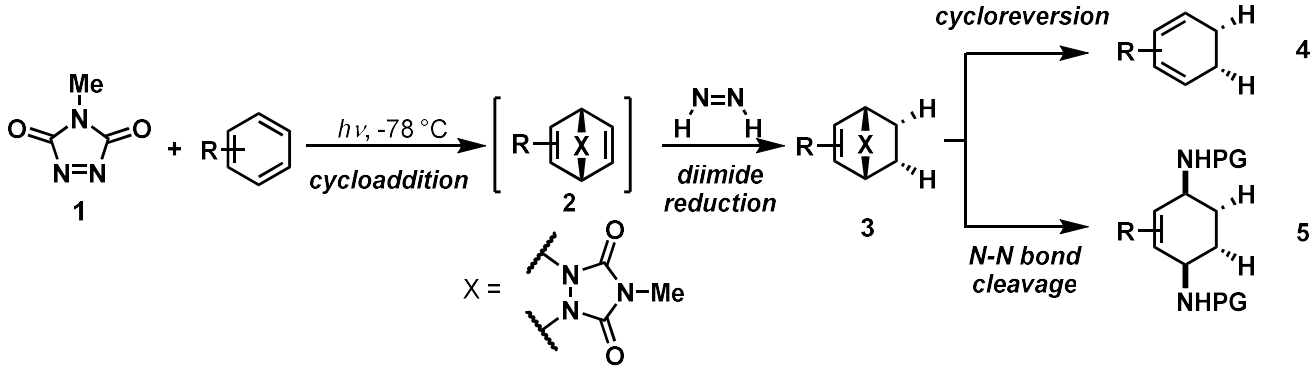


Figure 1. Reductive dearomatization of arenes with N-N arenophile, MTAD.

1.2. CYCLOADDITION

It was found that running the cycloaddition at -78 °C in EtOAc under visible light irradiation until the pink colour disappeared was optimal. The disappearance of the vibrant pink was an indication of the consumption of MTAD in the cycloaddition, and further chemistry was to be initiated. The diimide reduction was run at -50 °C for 5 h in the presence of acetic acid. Lower temperatures resulted in lower yields, likely because the diimide was not being generated.

When the optimized conditions for the diimide reduction of MTAD cycloadducts was determined, the scope of the cycloaddition was explored (Figure 2). A mixture of unseparable constitutional isomers were isolated and characterized, with the reduction of the less-substituted olefin product usually being the majority. The transformation was tolerant of many substrates containing: alkyl (**7, 8, 23, 25, 27**), halo (**9, 19, 21, 24**), silyl (**10**), ester (**11, 13, 14, 20, 22**), protected nitrogen (**12**), ketal (**16, 17, 18**) functional groups. Of note, biaryl product

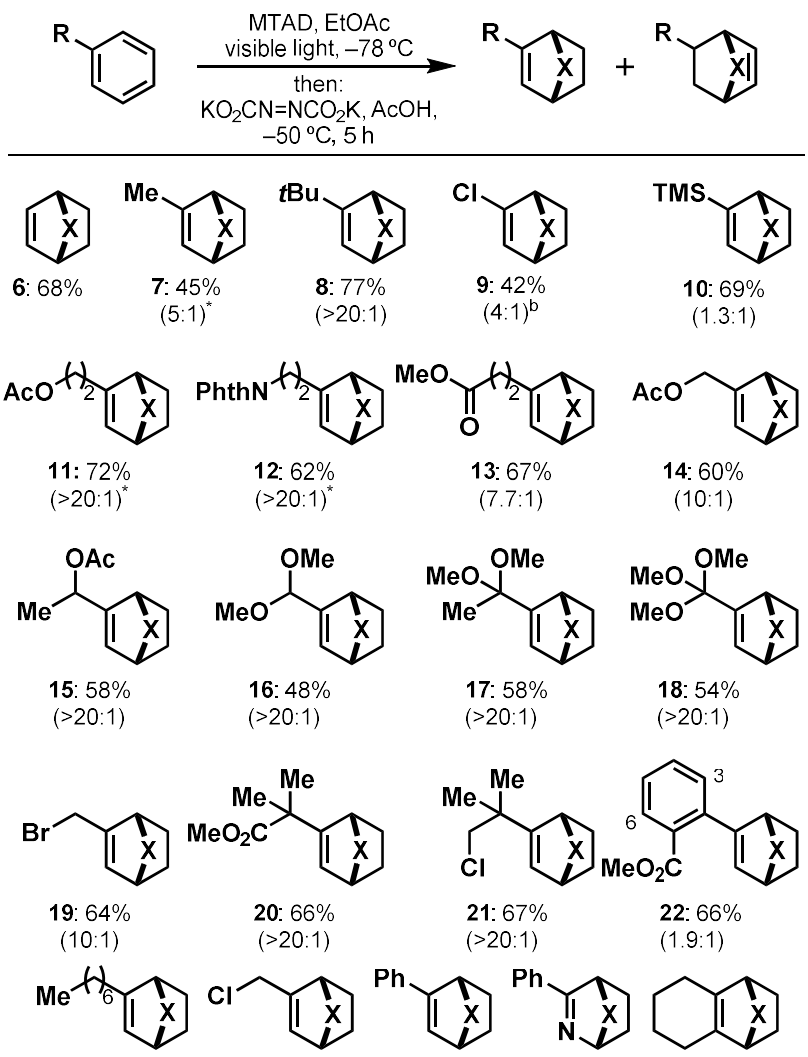


Figure 2. Substrate scope for cycloaddition for mononuclear arenes.

22 resulted in a 2:1 mixture of constitutional isomers across the 3,6-position of the more substituted arene.

An unexpected product isolated was **26**, where MTAD added across the pyridine ring, rather than the phenyl ring. Addition across the phenyl ring was not observed at all. Other pyridyl substrates were tested (Figure 3), but no cycloaddition was observed. It was expected that 3-phenylpyridine and 4-phenylpyridine would not give any product since cycloaddition across the 2,5-positions give trisubstituted olefins, which are difficult for diimide reduction. Disubstituted arenes gave very low yields (**27**) or no cycloaddition occurred at all in the case of *o-,m-,* and *p*-xylenes.

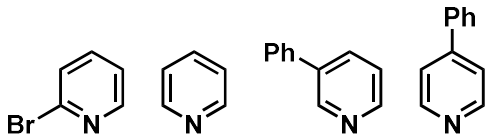


Figure 3. Pyridines tested.

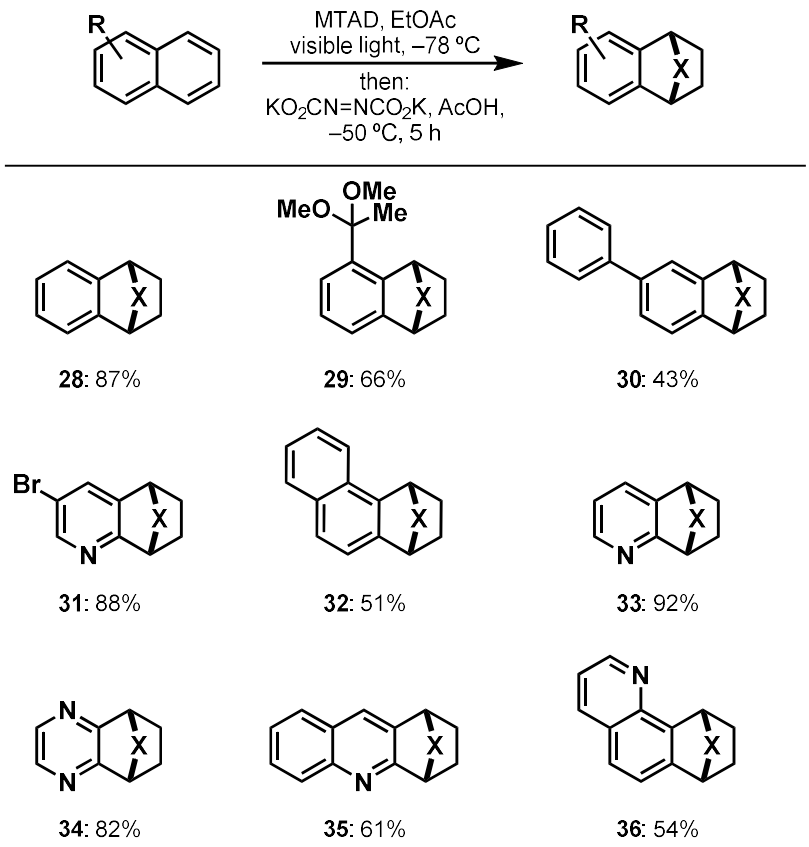


Figure 4. Substrate scope for cycloaddition of polynuclear arenes.

Cycloaddition of polynuclear arenes and heteroarenes proceeded in higher yields and shorter reaction times, due to the lower resonance stabilization energy per ring of these molecules (Figure 4). Cycloaddition across 2-phenylnaphthalene occurred selectively on the naphthalene ring, further away from the phenyl substituent. Nitrogen-containing heteroarenes:

quinoline (**33**), quinoxaline (**34**), acridine (**35**), and benzoquinoline (**36**), underwent cycloaddition in high yields. Dearomatizations of mononuclear and polynuclear substrates were very efficient and could be scaled up to a gram or more of MTAD (**11, 28**).

1.3. CYCLOREVERSION

In order to cyclorevert the reduced cycloadducts to cyclohexadienes, the urazole moiety must be removed, and the resulting cyclic hydrazine oxidized to diazo compound, for the retro[4+2] to occur (Figure 5).

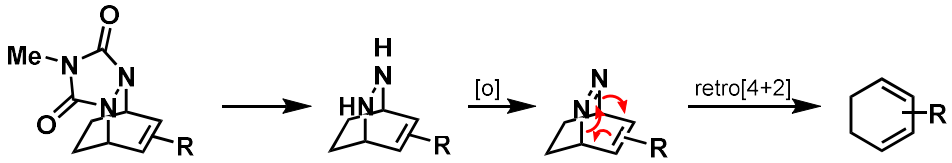


Figure 5. Cycloreversion of reduced cycloadducts to cyclohexadienes.

Hydrazine (monohydrate and anhydrous) was not a good base for the removal of the urazole. Residual hydrazine could not be removed, and interfered with the oxidation step with copper. Hydroxide bases were found to be the best base for this step. Hydroxide bases, KOH and NaOH, in protic solvents, MeOH and *i*PrOH, were tested at 60 °C, 80 °C, and 100 °C. It was found that higher temperatures lead to higher yields. KOH was a better base than NaOH. Methanol gave slightly higher yields than isopropanol; however, there were concerns about heating methanol to 100 °C, so isopropanol was the solvent of choice for the cycloreversion. After neutralization of base with acetic acid, addition of aqueous $CuCl_2$ oxidized the hydrazine immediately and the discontinuation of gas evolution was a sign of completion of cycloreversion. With optimized conditions in hand, the cycloadducts that could undergo cycloreversion were looked at (Figure 6). Alkyl (**37, 38**), silyl (**39,40**), and ketal (**45, 46, 47**) containing substrates were well tolerated. Esters were deprotected under basic conditions to reveal alcohols (**41, 43, 44**) or acids (**49, 51**). Primary amine **42** was unveiled from the *bis*-Boc protected cycloadduct **12**. *i*Propyl ether **48** was derived

from the corresponding bromide cycloadduct **19**. The only substrate containing a halide was **50**, since it was tertiary. Cycloadducts **8** and **9** and other primary and secondary halides gave an uncharacterized mixture of elimination and products.

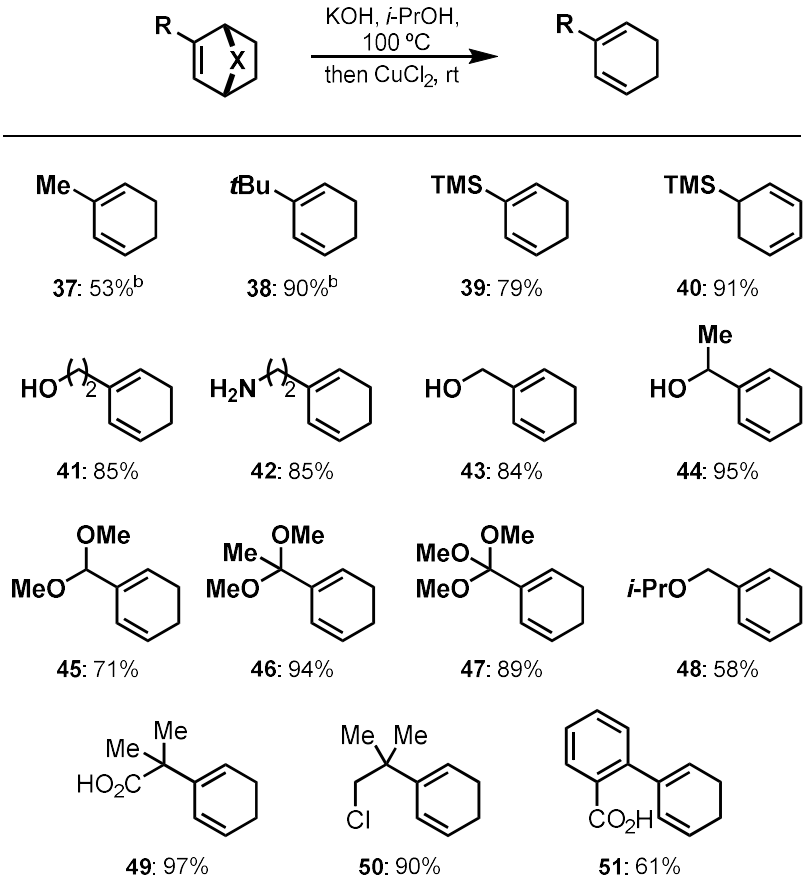


Figure 6. Substrate scope for cycloreversion.

1.4. *N-N* BOND CLEAVAGE

Fragmentation of the N-N bond for polynuclear substrates proceeded through the removal of triazolinedione moiety with hydrazine, followed by heterogeneous catalytic reduction of the N-N bond with Raney Nickel®.[6] Hydrogen was generated *in situ*, through catalytic degradation of hydrazine to hydrogen and nitrogen gas. Many polynuclear arenes and nitrogen-containing heterocycles were compatible with this method (Figure 7). Of note, pyridyl bromide **55** was tolerated. Protodehalogenation was seen with substrates based on naphthalene (**61, 62**) during

catalytic reduction, yielding **52**, so it was surprising the see it survive with the quinoline substrate, which is more electron-deficient and should facilitate oxidative addition of the nickel catalyst.

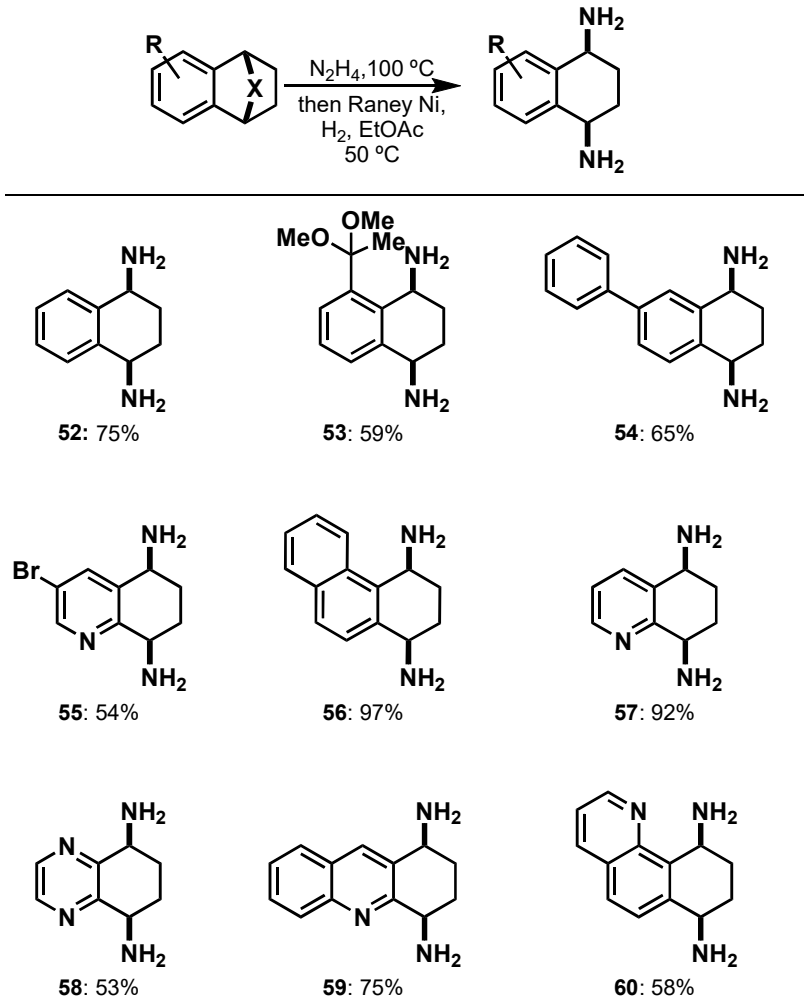


Figure 7. Substrate scope for *N-N* bond fragmentation of polynuclear substrates.

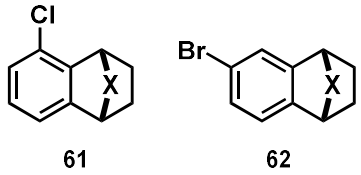


Figure 8. Cycloadducts that gave **52** during *N-N* bond cleavage through protodehalogenation.

1.5. SYNTHETIC APPLICATIONS

The utility of the dearomative reduction of arenes was showcased in the synthesis of bioactive marine natural product **63** (Figure 9).[7] In two steps from feedstock chemical, naphthalene, a compound of much greater value was synthesized. After isolation of the reduced cycloadduct, exposure to hydrazine gave the cyclic hydrazine substrate, which under oxidative and basic conditions, gave the Kornblum DeLaMare product **63**.

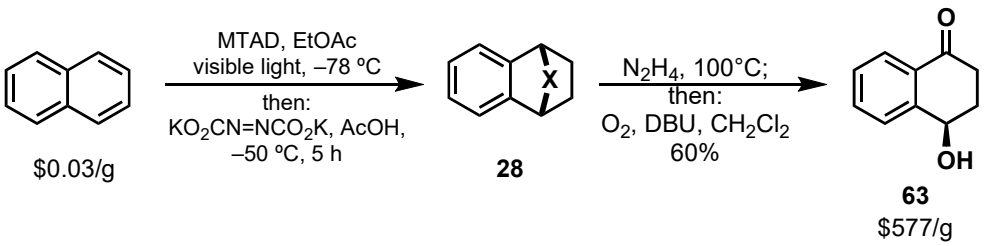


Figure 9. Synthesis of natural product **63** in two steps from naphthalene.

CHAPTER 2: STUDIES TOWARDS THE SYNTHESIS OF CARDIOTONIC STEROIDS CALOTROPIN AND CALACTIN

2.1. INTRODUCTION

Calotropin **64** and calactin **65** (Figure 10) are cardenolide steroids isolated from the milkweed of many genera of the Apocynaceae family, found in Africa, Asia, Europe, Australia, South America, and tropics of North America.[8] The first historical use of the milkweed was in African dart arrow poison, for their cardiac arresting properties, leading to death.[9] Calotropin is very active against multiple cancer cell lines, with IC_{50} values in the 1-2 nM range. Its cytotoxicity has been attributed to caspase activation and down-regulation of apoptotic proteins in the Wnt signaling pathway.[10] Their potent biological activities make calotropin and calactin attractive targets for total synthesis. The crystal structure of calactin has been obtained.[11]

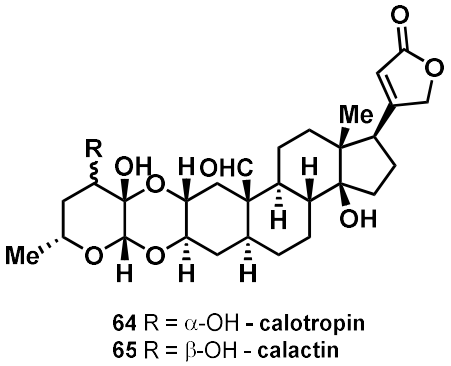


Figure 10. Structures of calotropin and calactin.

The structures of calotropin and calactin differ in the configuration of the stereocentre of the hydroxyl group off the sugar portion of the molecule. The dideoxypyran sugar portion of the molecule is connected to the steroid core through the dioxane ring, in a *cis, cisoid, trans*-fusion (Figure 11).

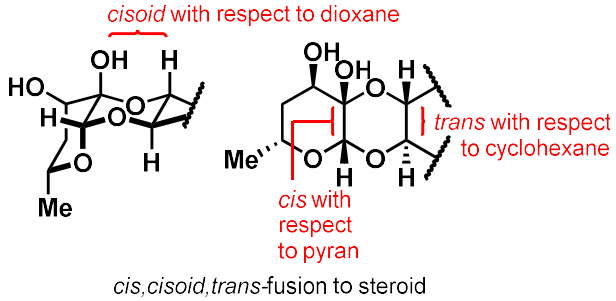


Figure 11. Connectivity of glycon portion to steroid.

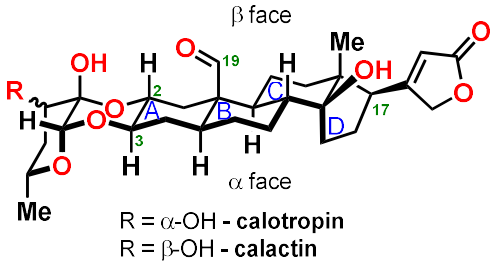


Figure 12. Structual features of calotropin and calactin.

The structures of the steroid cores of the molecule are unique to the cardenolide class, where a *cis*-CD ring fusion exists, rather than the standard thermodynamic *trans*-fusion (Figure 12). Two other notable features of the molecules are the C19 aldehyde, and C17 butenolide, both sensitive functionalities that should only be revealed towards the end of a synthesis.

2.2. SYNTHESIS OF OTHER CD-*cis* FUSED STEROIDS

Although calotropin and calactin have never been synthesized before, other CD-*cis*-fused steroids have been the targets of synthetic campaigns. Oubagenin **66**, has been synthesized semisynthetically and twice by total syntheses. The Deslongchamps' group was the first to synthesize oubagenin, using a polyanionic cascade to build the B and C in a total of 27 steps from their advanced intermediates (Figure 13).[12] Although oubagenin has many different features than calotropin, some of the strategies in appendment of the butenolide or installation of similar stereocentres can lend themselves to the synthesis of calotropin.

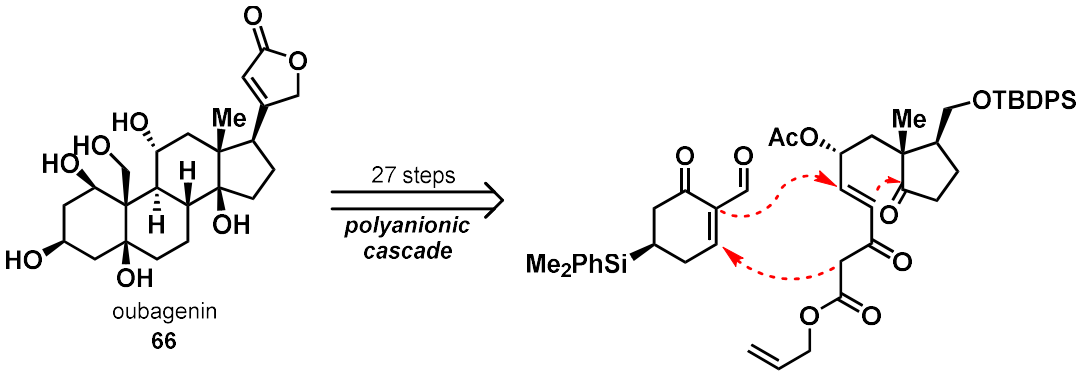


Figure 13. Deslongchamps total synthesis of oubagenin.

The Baran group synthesized oubagenin through a semisynthetic approach. They started with adrenosterone, and use the existing functional handles to direct in a site- and stereospecific, C-H oxidations at other positions, in what they termed a redox-relay approach (Figure 14).[13]

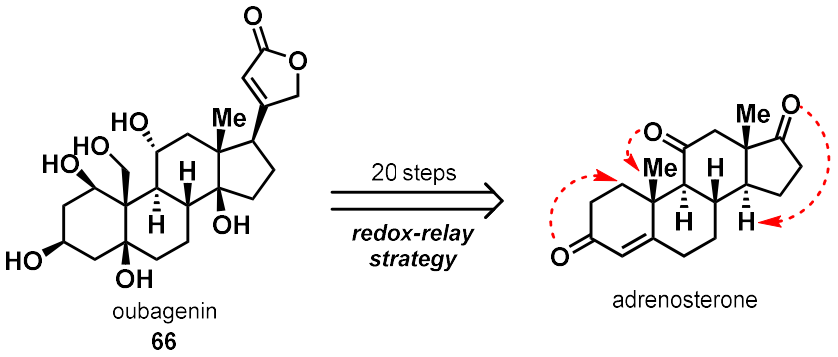


Figure 14. Baran's semisynthesis of oubagenin.

The most recent and shortest synthesis is from the Inoue group, albeit their starting materials were very advanced and took 15 steps to make from commercially available starting materials (Figure 15).[14] They made use of a radical conjugate addition of **67** into enone **68**, with the resulting enolate displacing the acetoxy group to close the C ring of the steroid.

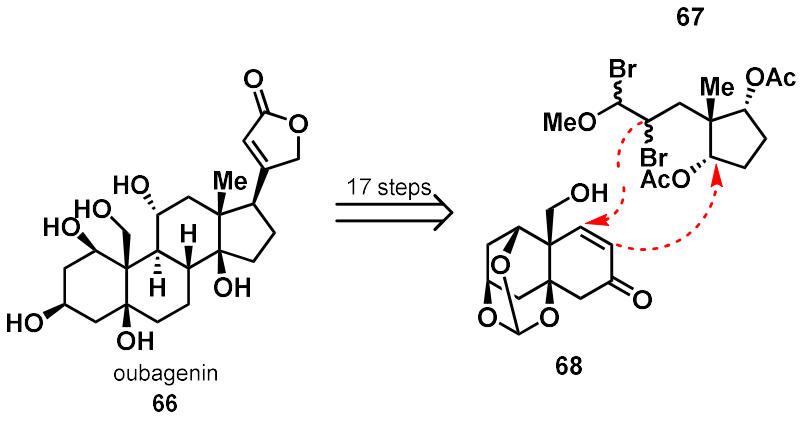


Figure 15. Inoue's synthesis of oubagenin.

Last year, the Nagorny group synthesized multiple steroids containing CD-*cis*-fused rings, in a highly convergent, efficient, and stereocontrolled manner (Figure 16).[15] In 7 steps, from commercially available starting materials, they build a steroid core which is common to many natural products. This common intermediate is then highly diversifiable, and allows them to reach several targets, shown below. In fact, this strategy could also potentially be used to build calotropin.

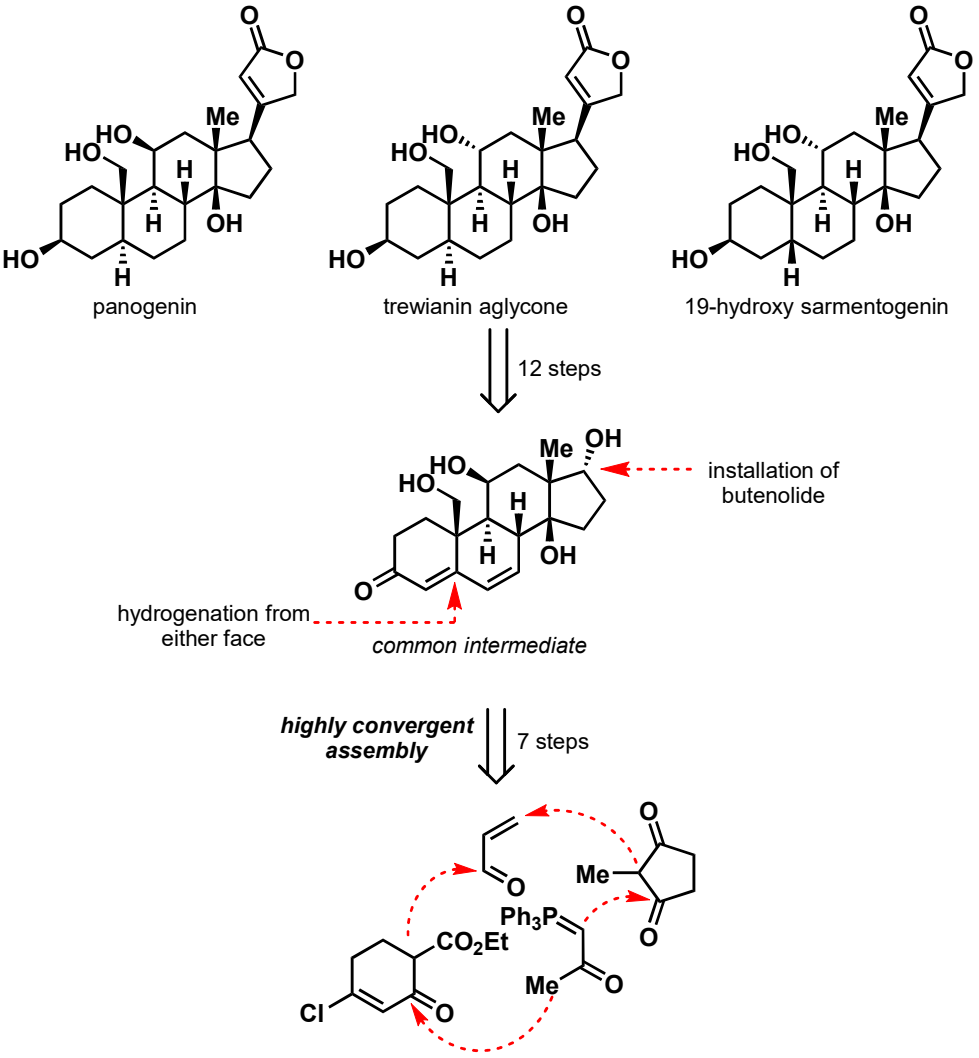


Figure 16. Nagorny's steroid syntheses.

2.3. RETROSYNTHETIC ANALYSIS

The focus of the retrosynthetic planning was the development of a steroid core synthesis that was original and highly convergent. The retrosynthetic analysis of calotropin **64**, outlined in Figure 17, begins with the disconnection of the glycon portion of the molecule, giving rise to the glycosylating reagent **69**, which is available in 7 steps from glucose, and C2,C3-*trans*-diol steroid **70**.[16] The *trans*-diol can be elaborated from dienone **71**, and installation of a butenolide on the D ring at C17.[12-15,17] The dienone was envisioned to be a product of an asymmetric intramolecular

palladium-catalyzed nucleophilic dearomatization of a phenol by the aryl bromide fragment **72**.[18] The dearomatization occurs through oxidative addition of the palladium catalyst into the vinyl-bromide or aryl-bromide bond, followed by nucleophilic attack of the *para*-position of the phenol upon the Pd(II) centre (Figure 18).[19] Subsequent reductive elimination of the cyclohexadienone and arene yield the dearomatized product and regenerates the catalyst. This transformation was previously utilized in the synthesis of triptoquinone H and its epimer by the same group that developed the methodology. Disconnection of the phenol and vinyl bromide gives rise to styrene **74** and bicyclic dione **73**. The latter may be traced back to linear aldehyde precursor **75** through an asymmetric NHC-catalyzed benzoin condensation.[20]

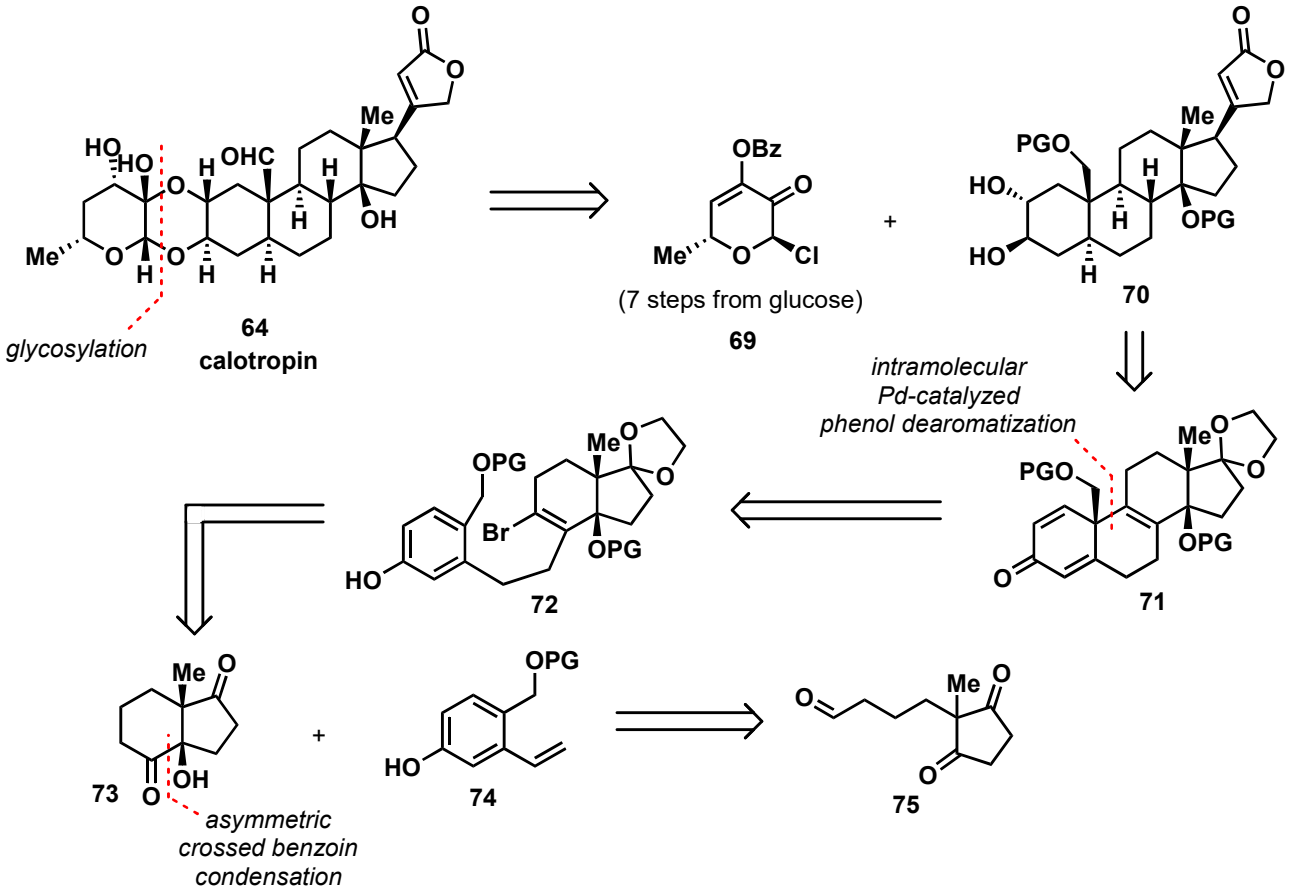


Figure 17. Retrosynthetic analysis of calotropin.

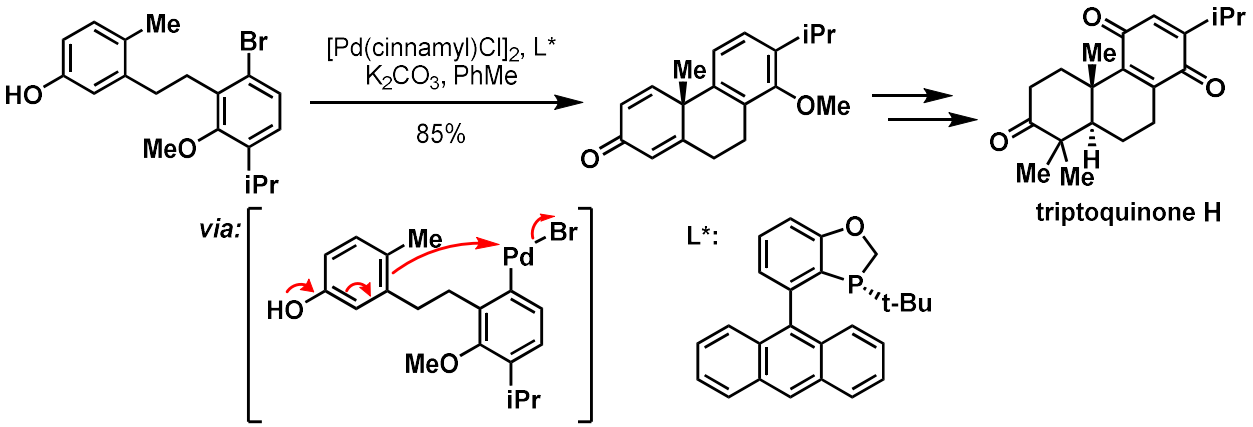


Figure 18. Asymmetric Pd-catalyzed phenol dearomatization in synthesis of triptoquinone H.

2.4. APPROACHES TOWARDS THE CD RINGS

The first goal of the project was amassing large quantities of dione **73**, to try multiple routes to the steroid core. Known strategies to synthesize linear precursor **75**, involve alkylation of 2-methyl-1,3-cyclopentadione (**76**) with an activated C4-electrophile, followed by functional group interconversions. The equilibrium state of 2-methyl-1,3-cyclopentadione is primarily the β-hydroxyenone (Figure 19), therefore O-alkylation predominates over C-alkylation unless an activated electrophile or Michael acceptor is used.

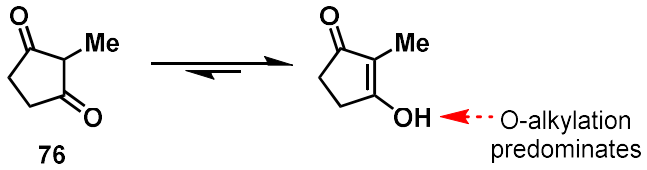


Figure 19. Tautomeric forms of 2-methyl-1,3-cyclopentadione.

The published procedure to the linear precursor to benzoin condensation intermediate **75**, was followed; however, there were difficulties in the purification of synthetic intermediates (Figure 20).[21] The route commenced with the radical bromination of methyl crotonate **77** to yield allylic bromide **78**, which was purified through distillation. Reduction of the methyl ester to the allylic alcohol **79** with DIBAL appeared to give clean conversion by TLC and with some impurities

by crude NMR. Attempts to purify allylic alcohol by column chromatography resulted in complete degradation of the product, presumably by polymerization of the allylic bromide.

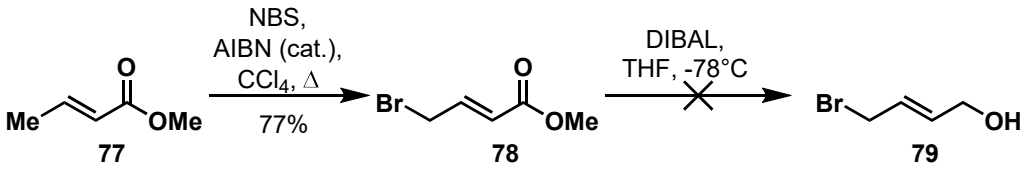


Figure 20. Attempted synthesis of allylic bromide **79**.

Attempts to carry the crude allylic alcohol forward by protecting the allylic alcohol with THP and TBS protecting groups were not fruitful (Figure 21). The same problem with column chromatography as in the case with the unprotected allylic alcohol was encountered.

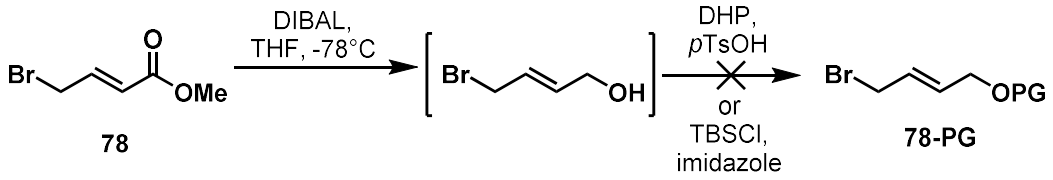


Figure 21. Synthesis of protected allylic alcohol **78-PG**.

Michael addition of 2-methyl-1,3-cyclopentadione into acrolein to yield aldehyde **79** is a well-known, high-yielding process (Figure 22). Aldehyde **79** has been shown to undergo Wittig olefination, so it was hypothesized that aldehyde **79** could be homologated using a methoxymethylphosphonium halide **80**.[15] A screening of bases yielded no desired product **81**; only cross aldol products were detected.

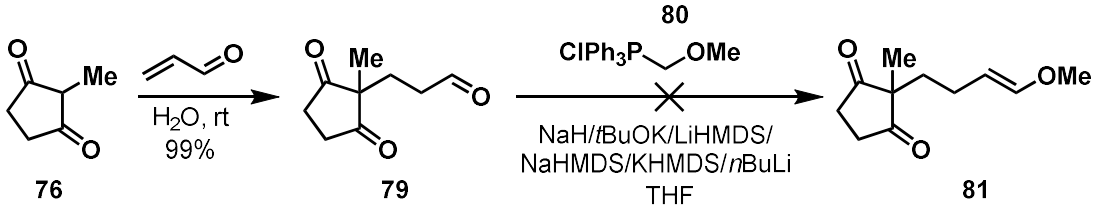


Figure 22. Attempted homologation of aldehyde **79** using Wittig olefination.

An *in situ* hydrolysis of methyl vinyl ether **81** from Wittig oleftination also gave no desired aldehyde **82** (Figure 23).

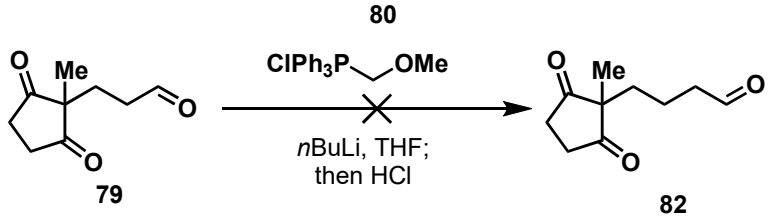


Figure 23. Wittig olefination and *in situ* hydrolysis of aldehyde **79**.

The Horner-Wittig variant of the Wittig olefination, utilizing a phosphate olefinating reagent, was attempted, but no β-hydroxyphosphate **83** was detected (Figure 24). *In situ* elimination of the oxaphosphetane with base did not yield the desired vinyl methyl ether **81** (Figure 25).

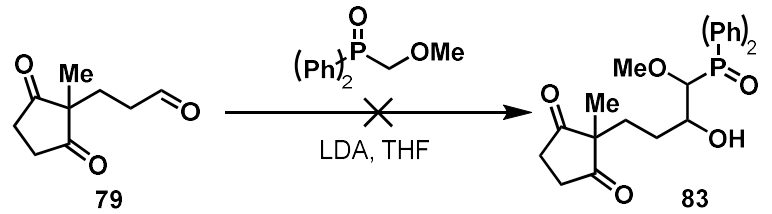


Figure 24. Horner-Wittig addition into aldehyde **79**.

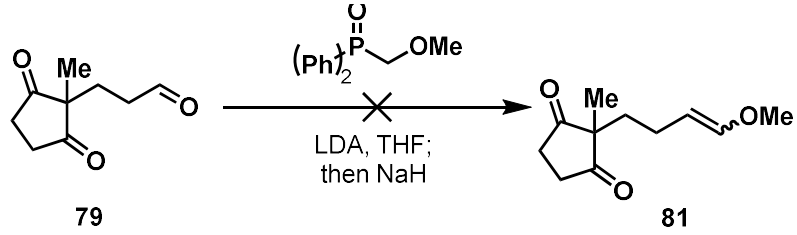


Figure 25. Horner-Wittig olefination of aldehyde **79**.

Attempts to homologate aldehyde **79** were abandoned for the original strategy of alkylation of cyclopentadione **76** with an activated electrophile, but a different route to the alkylating reagent was pursued. Beginning with THP protection of propargyl alcohol **84** to deliver terminal acetylene

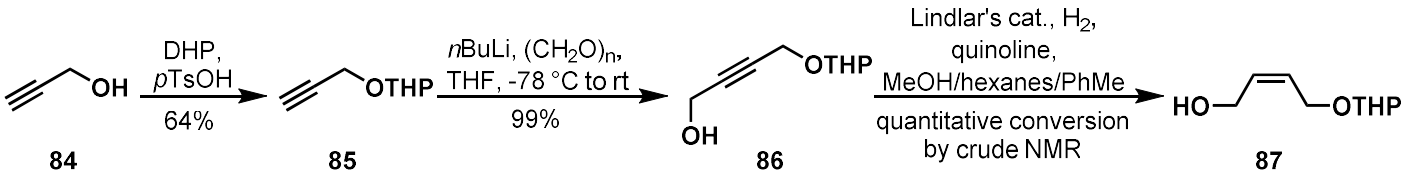


Figure 26. Synthesis of monoprotected butenediol **87** from propargyl alcohol.

85, the alkyne was deprotonated with *n*BuLi and quenched with paraformaldehyde in a Favorskii reaction to afford the monoprotected diol **86** (Figure 26). A Lindlar reduction of alkyne **86** in a variety of solvents, with careful monitoring by crude NMR of aliquots showed complete conversion to the allylic alcohol **87**. Although this route was high-yielding, scalable, and quick, it was abandoned due to the commercial availability of *cis*-butene-1,4-diol **88**.

The final approach taken to synthesize aldehyde **75** is shown in Figure 27. The viability and scalability of each step was determined for a series of protecting groups: THP, TBS, and Bn.

Due to the acid-lability of the THP group, analysis of reactions by TLC proved to be difficult. Despite this problem, milligram quantities of aldehyde **75** could be obtained by the end

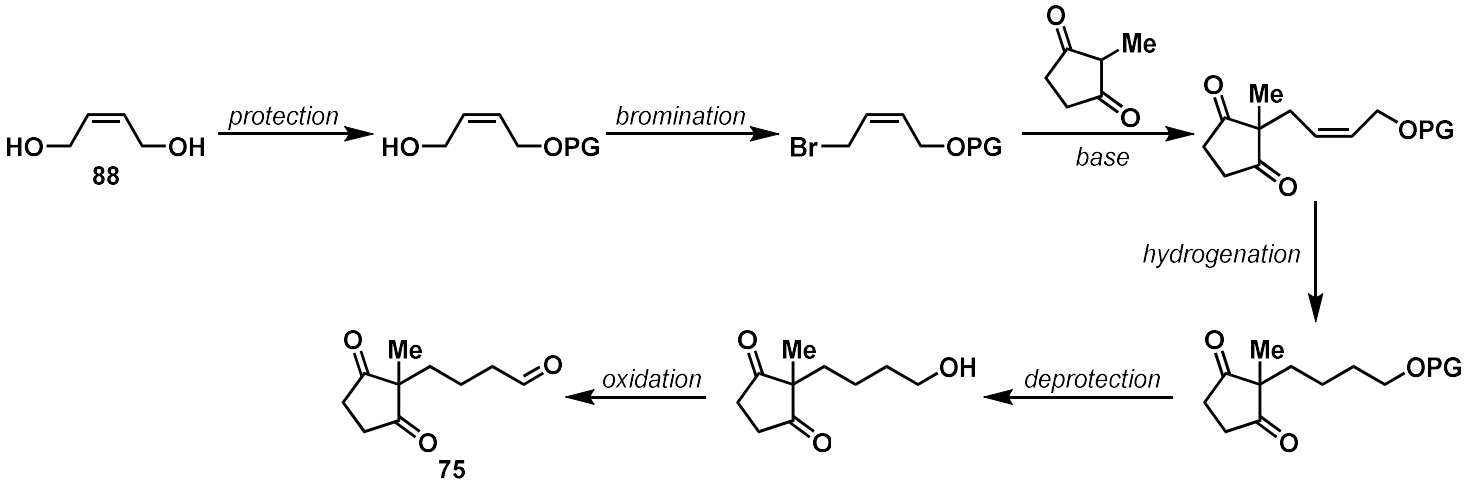


Figure 27. General route to aldehyde **75**.

of the sequence. The alkylation step, deprotonation of the cyclopentadione **76** with NaH in DMF, followed by dropwise addition of the allylic bromide, was not scalable. At test scales, a moderate yield of 60% could be obtained, but scales above 300 mg resulted in 0 to 30% yield of desired product. O-alkylation product accounted for most of the mass recovery, but as scales went above 1 g, most of the mass was not recovered.

Use of the TBS protecting group in the synthesis did not come with the same TLC analysis problems as the THP group, but the early bromination step was rate-limiting. Multiple conditions

were tried: mesylation followed by bromination with LiBr in DMF, bromination with PBr_3, and an Appel reaction. The Appel reaction was quantitative on small scales, but when the scale was increased, an uncharacterized byproduct which co-eluted with the desired product was formed. When this mixture of products was exposed to alkylation conditions, minimal alkylation product was detected.

The benzyl protecting group proved to be the most efficient of the protecting groups based on overall yield, scalability, and the combination of hydrogenation and deprotection steps (Figure 28). The monoprotection of diol **88** proceeded with NaH in THF followed by treatment with BnBr in a 90% on a 20 g scale. Allylic bromide **90** was then prepared from alcohol **89** under Appel conditions on a 18 g scale in 77% yield. This was used as the alkylation agent in the presence of NaH in DMF with cyclopentadione **76**. On a 2 g scale, the reaction went to completion, with a yield of 37%, but on a 3 g scale, with higher equivalents of base, there was incomplete consumption of cyclopentadione, and as a result, a lower yield of 23%. Parallel hydrogenation and

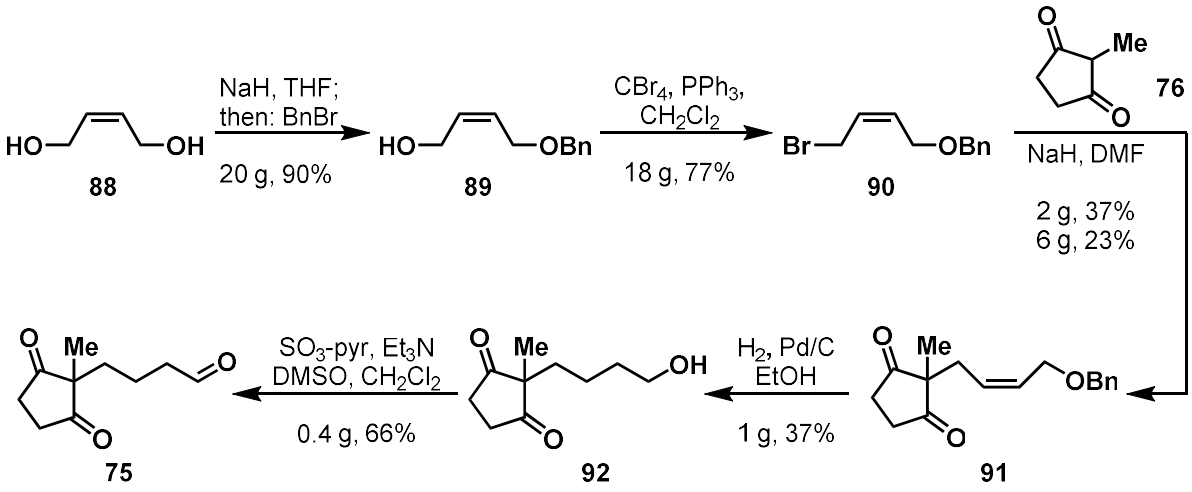


Figure 28. Synthesis of aldehyde **75** using benzyl protecting group.

hydrogenolysis of the benzyl group with Pd/C under a H_2 atmosphere provided the primary alcohol **92**, which was then oxidized under Parikh-Doering conditions to give aldehyde **75**.

With aldehyde **75** in hand, the aldehyde–ketone, intramolecular benzoin condensation was attempted, the mechanism of which is shown in Figure 29. Deprotonation of the NHC salt generates the active carbene catalyst, which adds into the aldehyde. The Breslow intermediate is formed by tautomerization, and the resulting enamine attacks into the ketone which is an overall *umpolung* addition of aldehyde into the ketone. Elimination of the NHC catalyst to generate the product ketone and carbene catalyst completes the cycle.

The benzoin condensation was attempted with a variety of reported conditions with bases Et_3N, Cs_2CO_3, and DBU, solvents THF, tBuOH, and EtOH, and at 60 °C.[22] Commercially available thiazolium catalysts **93** and **94** were shown to catalyze the intramolecular benzoin condensation on similar substrates, so it seemed likely it would work on aldehyde **75**, but no desired product was detected. The reported achiral and chiral triazolium catalysts **95** and **96** were difficult to obtain due to the required high quality Meerwein's salt to synthesize them. [23] The total synthesis route stopped at this point in favour of the semi-synthesis reported in Chapter 2.5.

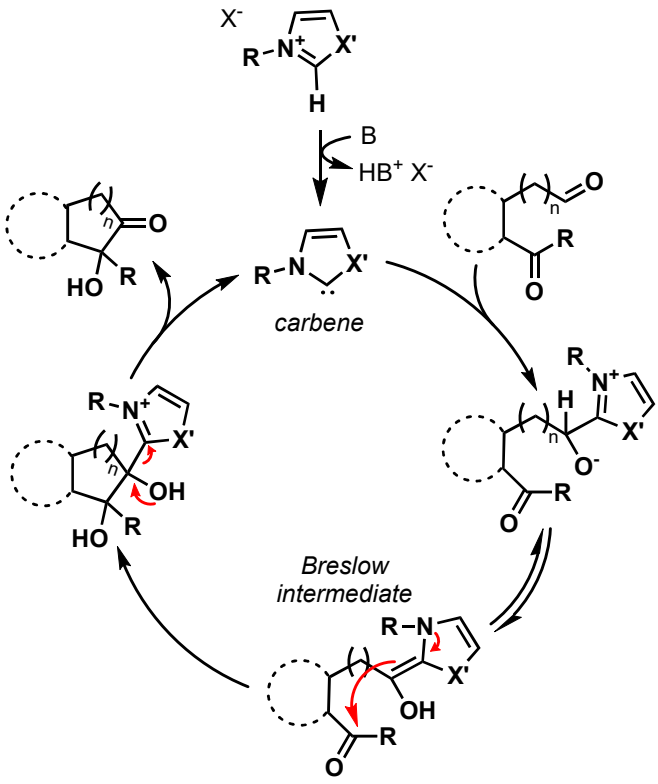


Figure 29. Catalytic cycle of NHC-catalyzed intramolecular aldehyde-ketone benzoin condensation.

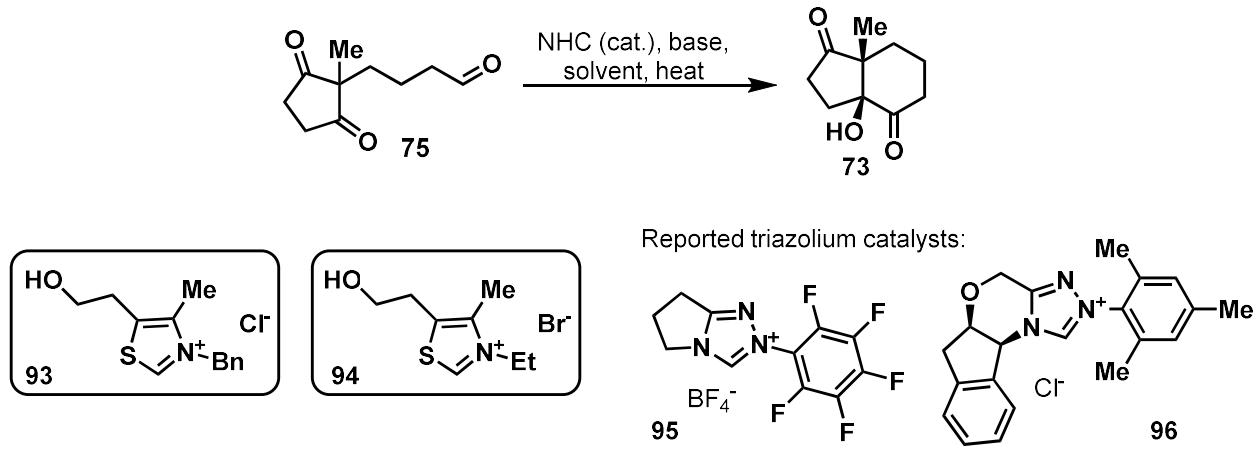


Figure 30. Attempted benzoin condensation of aldehyde **75**.

2.5. SEMI-SYNTHESIS

An alternative to a novel synthesis of the steroid core was the semi-synthesis from a commercially available steroid. With most of the carbon skeleton in place, the synthesis would focus on chemo- and stereoselective oxidations. An attractive candidate to begin the synthesis was the abundant and cheap estrone. The only semi-synthesis in which estrone was utilized, was a cortistatin core synthesis by the Corey group, where the B-ring was expanded.[24] The Baran group also attempted to dearomatize estrone in their synthesis of oubagenin.[17] They found that the original report for the dearomatization at the *para*-position with a C1 source had incorrectly characterized the orthoquinone product **98** as the desired **97** (Figure 31).[25]

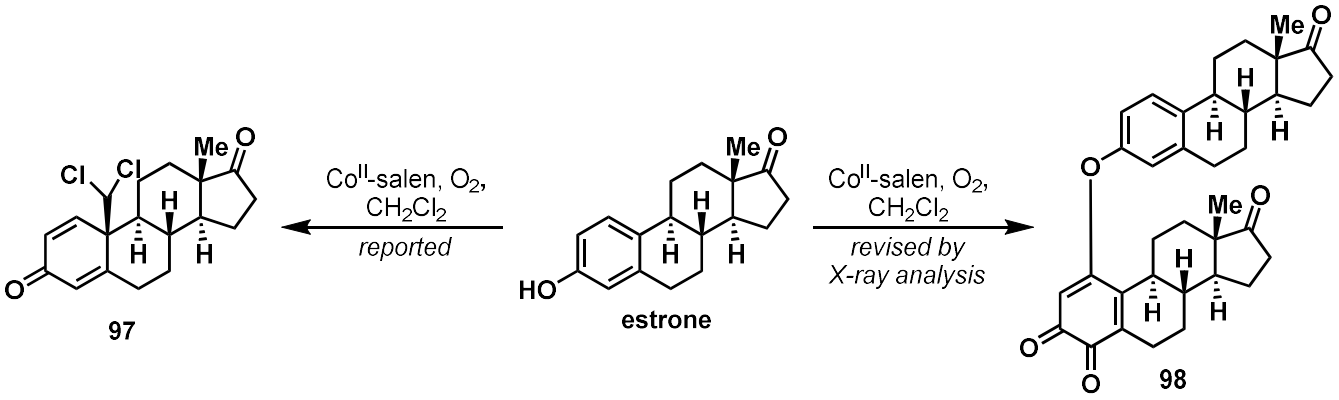


Figure 31. Baran group structural revision of estrone dearomatization strategy.

A method to dearomatize phenols selectively and in high yields at the *para*-position with a C1 source, known as an angular methyl group, would be a powerful strategy for the synthesis of calotropin from estrone, and in general. The known methods to achieve this transformation are non-selective, low-yielding, or required biased substrates (Figure 32). The first attempt at introducing the angular methyl group was from Woodward, who witnessed installation of a dihalomethyl group in the *para*-position of the phenol **99**, as a byproduct of the Reimer-Tiemann reaction (Figure 32A).[26] The *ortho*-formylated product **100** consisted of the majority of the product distribution. A higher yielding strategy is the oxidative dearomatization of phenol with $PhI(OAc)_2$ as the oxidant, and an allylsilane as the nucleophile (Figure 32B).[27] The requirement for this reaction to occur selectively is the use of *ortho* blocking groups. High yields are only achieved when *tert*-butyl groups are used in both *ortho*-positions. The last known strategy is the nucleophilic dearomatization of phenols with allyl halides as the electrophile in the presence of silver salts (Figure 32C).[28] This was used to synthesize a starting material for another methodology and was low-yielding due to the preferential *ortho*-Friedel Crafts alkylation. The allyl group can

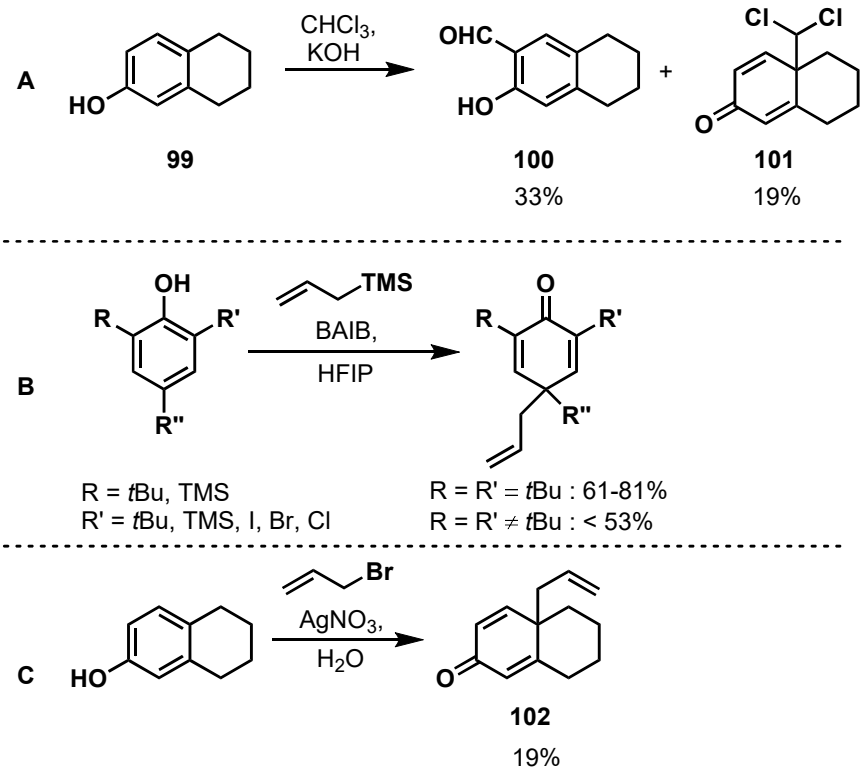


Figure 32. Installation of angular methyl group. A - Reimer Tiemann byproduct; B - oxidative dearomatization; C - nucleophilic dearomatization.

be considered a protected C1 carbon source. The aldehyde can be revealed through isomerization of the terminal olefin, followed by oxidative cleavage of the internal olefin.

The retrosynthetic analysis for the semi-synthesis of calotropin from estrone using the dearomatization strategy is shown below in Figure 33. The first disconnections removing the dideoxy sugar and butenolide are the same as the retrosynthesis in Chapter 2.3, which takes calotropin back to diol **130**. The diol can be traced back to dienone **104** through the removal of the oxidation at C14. Dienone **104** can then be envisioned as a dearomatized product of estrone.

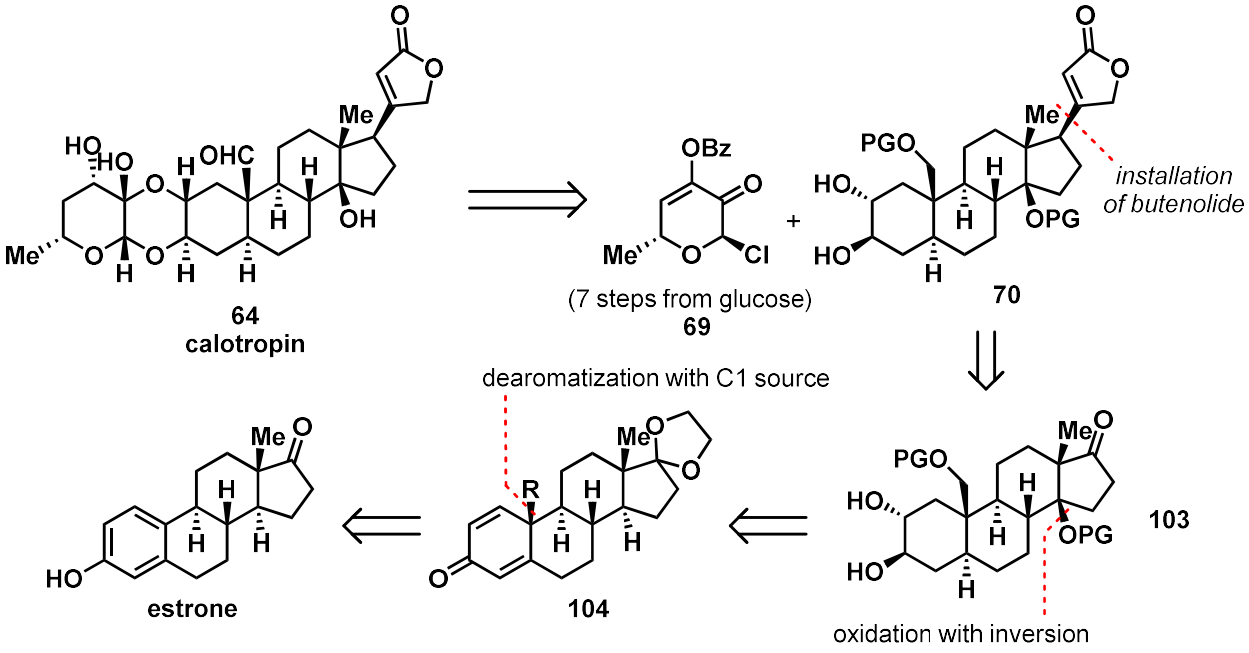


Figure 33. Retrosynthetic analysis for semisynthesis from estrone.

The dearomatization of estrone A ring is reminiscent of the biosynthesis of estrone in reverse, from commercially available androstenedione (Figure 34).[29] Androstenedione is oxidized by a P450 cytochrome enzyme at the C19 position to 19-hydroxyandrostenedione, which is also commercially available. This would be a desirable intermediate to reach in the semisynthesis and

allows for the parallel exploration of the dearomization strategy and further synthesis of calotropin from the dearomatized intermediate. 19-hydroxyandrostenedione is further oxidized by P450s twice to release formic acid and aromatize the A ring to yield estrone.

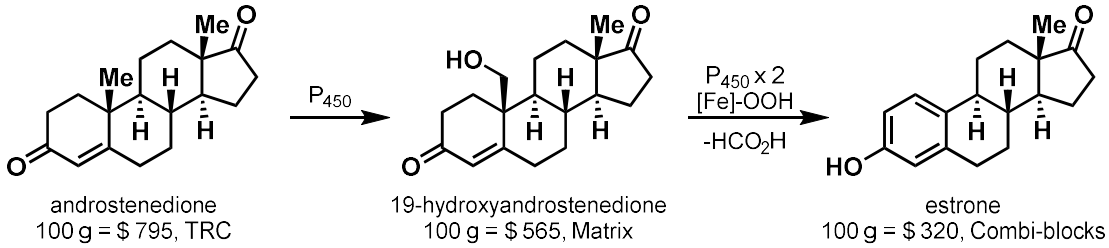
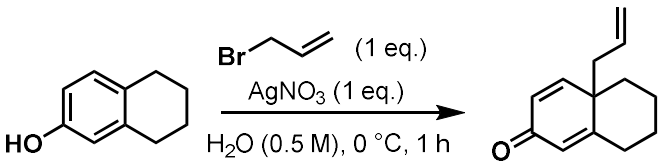


Figure 34. Biosynthesis of estrone from androstenedione.

2.6. ESTRONE DEAROMATIZATION

With the start point for the nucleophilic dearomatization of the tetrahydronaphthol **99** using allyl bromide and silver salts in Figure 32C, an optimization was attempted. The silver salt abstracts the halide, generating a soft allyl cation electrophile. Attack of the phenol should in theory occur at the *para*-position, where the highest HOMO coefficient should reside, furthest away from the hard oxygen functionality.

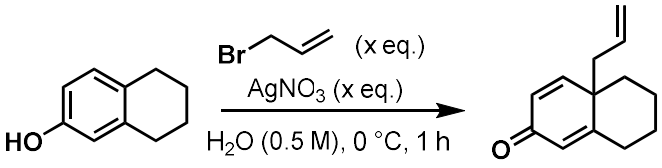
Optimization began with the standard conditions as reported by the Xie group (Table 1 Entry A).[28] The crude NMR was extremely difficult to interpret. Desired product peaks could not be distinguished from byproducts, so purification was necessary, and isolated yields were determined for screens. Change of order of addition to addition of allyl bromide last (entry B) improved the yield from 8% to 17%, which was closer to the reported yield of 19%. Increased equivalents of both silver and allyl bromide asymptotically increased the yield to 21% at 2 equivalents although this made



Entry	Order of addition	% yield (isolated)
a	Ag last	8%
b	Br last	17%

Table 1. Order of addition experiments.

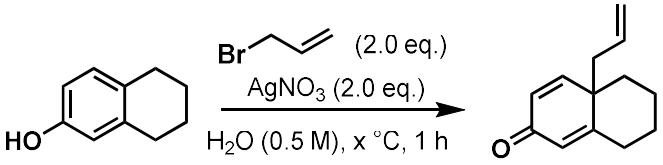
purification of the product more difficult (Table 2). Many more side products were seen by TLC, with close R_f's to the desired product, although they weren't characterized by NMR.



Entry	x	% yield (isolated)
c	1.0	8%
d	2.0	21%
e	5.0	21%
f	10	21%

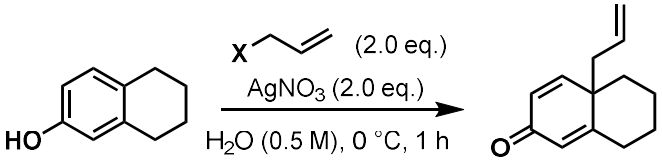
Table 2. Stoichiometry of reagents.

The stoichiometry was kept at 2 equivalents of both silver and allyl bromide from this point to maximize the yield of desired product. The reaction temperature was then explored (Table 3). The yield decreased exponentially as the temperature was increased from 0°C. Temperatures lower than 0 °C were not explored at this point, since water was the solvent.



Entry	x	% yield (isolated)
g	0	18%
h	25	6%
i	40	0%
j	100	0%

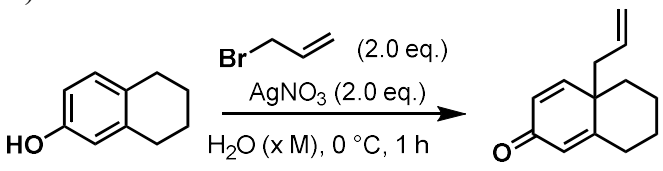
Table 3. Reaction temperature.



Entry	x	% yield (isolated)
k	Br	19%
l	Cl	0%
m	I	11%

Table 4. Allyl halides.

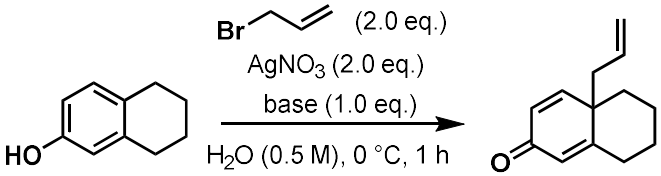
Different allyl halides were then explored, with allyl bromide shown to be the best in terms of yield, and availability (Table 4). It also seemed like the more concentrated the reaction, the higher the yield (Table 5).



Entry	x	% yield (isolated)
n	0.5 M	18%

Table 5. Concentration.

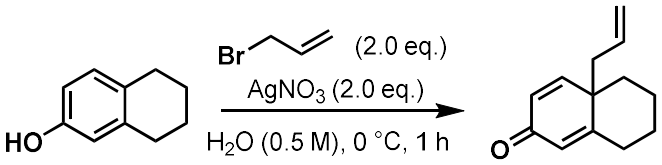
The role of Brønsted bases was explored (Table 6). When amine bases were added (Entries s and t), Ag(0) crashed out of solution and coated the walls of the vials immediately. When hydroxide bases were used, black precipitate, presumably Ag_2O crashed out of solution. The yields of the reactions in the presence of hydroxide base were lower than without. It was hypothesized that having a bulky tetrabutylammonium counterion associated with the phenoxide could block *ortho*-position, resulting in selective *para*-functionalization, but the yield of desired product was as low as using NaOH.



Entry	base	% yield (isolated)
q	NaOH	9%
r	Bu_4NOH	8%
s	Et_3N	0%
t	DIPEA	0%

Table 6. Brønsted bases.

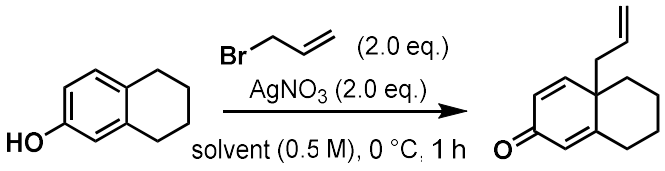
Slow addition of allyl bromide over 30 minutes was attempted, but the small volume made it very difficult to portion (Table 7). It is also immiscible with water, so a stock solution could not be made. An aqueous solution of silver nitrate was prepared and added slowly over 30 minutes. Neither of these experiments lead to an improved yield over a single addition.



Entry	Note	% yield (isolated)
u	add Br 30 min	5%
v	add Ag in H_2O 30 min	0%

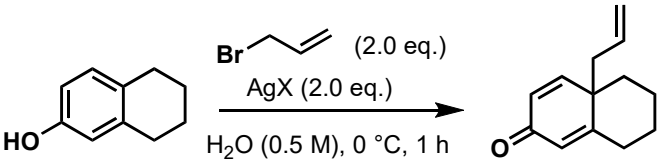
Table 7. Slow addition.

A series of organic solvents were screened (Table 8). HFIP and TFE, solvents known to stabilize charged intermediates, were tested, with only TFE (Entry x) giving product. No other organic solvent gave notable results. Mixtures of solvents miscible with water were also tested. A 1:1 mixture of dioxane and water (Entry ak) gave product.



Entry	Solvent	% yield (isolated)
w	HFIP	0%
x	TFE	18%
y	DMF	0%
z	MeCN	0%
aa	dioxane	2%
ab	acetone	0%
ac	CH_2Cl_2	11%
ad	AcOH	10%
ae	$MeNO_2$	10%
af	DMSO	0%
ag	PhMe	10%
ah	MeOH	0%
ai	Et_2O	0%
aj	EtOAc	12%
ak	dioxane/H_2O (1:1)	17%
al	MeCN/H_2O (1:1)	3%
am	HFIP/H_2O (1:1)	0%
an	TFE/H_2O (1:1)	0%
ao	DMF/H_2O (1:1)	7%

Table 8. Organic solvents and solvent mixtures.

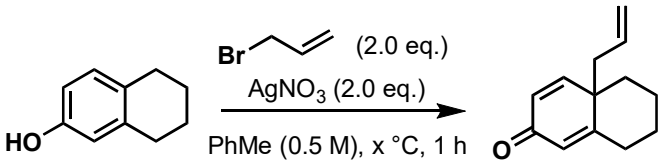


Entry	Solvent	% yield (isolated)
ap	Ag_2O	12%
aq	AgOTF	8%
ar	AgTFA	0%
as	$AgBF_4$	0%
at	$AgClO_4$	0%
au	$AgPF_6$	0%
av	$AgSbF_6$	0%
aw	$AgNTf_2$-MeCN	0%
ax	Ag(fod)	11%
ay	AgOAc	13%
az	Ag_2CO_3	15%
ba	AgOBz	0%
bb	AgNPhth	0%

Table 9. Silver salts.

Different silver salts were screened (Table 9). None of gave as high of a yield as $AgNO_3$, but Ag_2CO_3 (Entry az) and AgOAc (Entry ay) were close.

An organic solvent with low melting point, toluene was chosen, and temperatures lower than 0 °C were tested (Table 10). 0 °C proved to be the optimal temperature to run this reaction (Entry be).



Entry	x	% yield (isolated)
bc	-78	0%
bd	-20	10%
be	0	15%
bf	40	0%

Table 10. Low temperatures.

Optimizations attempts for this silver-mediated nucleophilic dearomatization did not result in yields higher than reported and there was no reduction in the number of observed byproducts. The best set of conditions were tested on ketal-protected estrone to see if the reaction would work at all, but no desired product was detected (Figure 35).

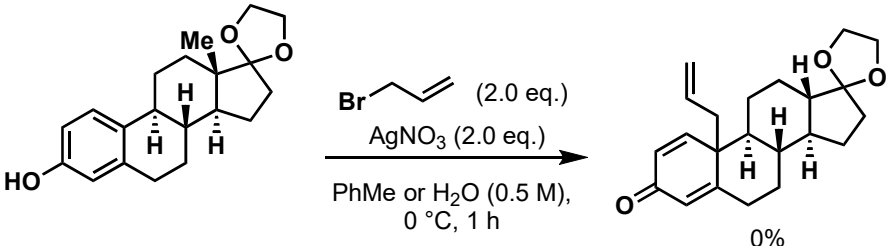


Figure 35. Nucleophilic dearomatization of protected estrone.

Dearomatizations of estrone and phenols at the *para*-position with oxygen has been very well characterized.[30,31] Estrone and estrogen are shown to have anti-oxidant properties, and capture hydroxyl radicals at the C10 position selectively.[32] This position was calculated to be the radical frontier position. Carbon-centred radicals generated in a reaction mixture in the presence of estrone should also go to this position.

A transformation that generates carbon centred radicals are the Zn-sulfinate radical C-H functionalization of heterocycles developed by the Baran group.[33] There were no phenols reported in the substrate scope, so this methodology was tried on naphthol **99** (Figure 36). No reaction occurred, and there was near quantitative recovery of starting material.

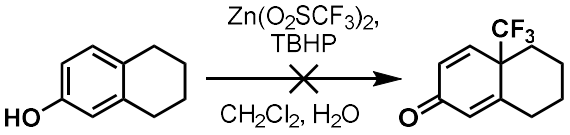


Figure 36. Dearomative trifluoromethylation of naphthol **99**.

2.7. FUTURE DIRECTIONS

Future work on this project can focus on the generation of carbon centered radicals for the dearomative functionalization of estrone, or the generation of a radical on estrone at C10. Dearomative hydroxylation of the *para*-position followed by formation of a Barton ester or redox-active ester forms a radical precursor that can be functionalized with photoredox coupling or nickel catalysis (Figure 37).[34]

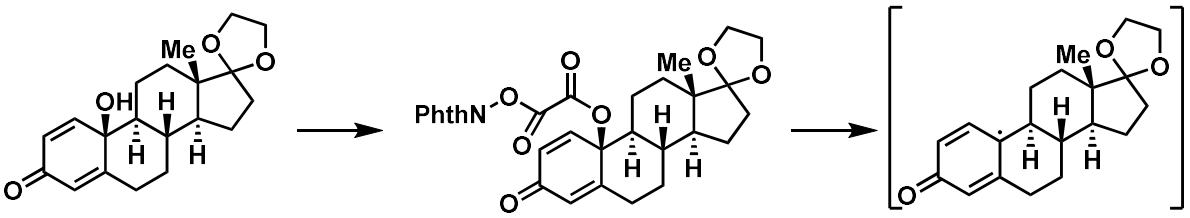


Figure 37. Formation of radical at C10 of estrone.

Another potential way to dearomatize estrone with an allyl group, is to allylate at another position, then isomerize to the *para*-position with multiple [3,3]-rearrangements.[35]

The route from 19-hydroxyandrostenedione to calotropin must also be determined and optimized. The steps to installation oxidation at C17, the butenolide, and dideoxy sugar have been done on similar systems, but reducing the number of steps in these sequences is highly desirable.

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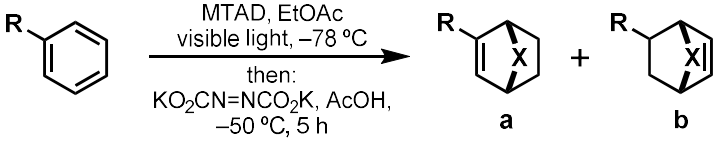
APPENDIX: SUPPLEMENTARY INFORMATION

Mononuclear arene cycloaddition



MTAD (**1**, 113.1 mg, 1.0 mmol, 1.0 eq.) was placed in a test tube. Ethyl acetate (10 mL, 0.1 M) was added to the test tube at – 78 ºC, followed by the addition of arene (10 mmol, 10 eq.). The mixture was then stirred under the irradiation with LED lights at –78 ºC until full decolorization of the reaction mixture was observed (pink solution to colorless solution). At –78 ºC, potassium azodicarboxylate (582.7 mg, 3.0 mmol, 3.0 eq.) was added in one portion, followed by the addition of acetic acid (0.86 mL, 15 mmol, 15 eq.) in ethyl acetate (4.0 mL). After stirring the resulting suspension at –50 ºC for 5 h, the reaction was warmed up to rt in a water bath, then quenched with water (2 mL). Saturated aqueous sodium bicarbonate solution (7.5 mL) was added, and then the organic phase was separated. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with saturated aqueous sodium chloride solution (15 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. After a short column of the crude material to remove the excess arene, the ratio of **a** to **b** was determined by ^{1}H NMR analysis. The mixture of compound **a** and **b** was then isolated by flash column chromatography (SiO_2, *n*-hexane/EtOAc mixture). For the spectroscopic characterizations of compound **3**, column-inseparable mixtures of solid products **a** and **b** were further purified by recrystallization from *n*-hexane/ethyl acetate mixtures, and only the major product **3** was characterized. For column-separable mixtures, both products **a** and **b** compounds were further separated by column chromatography, and characterized individually.

6

Synthesis of 6: The title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a white solid (131.3mg, 68%).

$\mathbf{R_f}$ = 0.18 (*n*-hexane:EtOAc = 2:1, UV, $KMnO_4$).

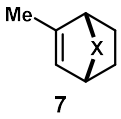
1H NMR: (500 MHz, $CDCl_3$) δ 6.42 (dd, *J* = 4.3, 3.1 Hz, 2H), 4.85 (ddd, *J* = 4.3, 3.1, 1.8 Hz, 2H), 3.00 (s, 3H), 2.20 – 2.11 (m, 2H), 1.56 (ddd, *J* = 11.2, 3.5, 1.8 Hz, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.1, 130.4, 50.2, 25.4, 22.1.

HRMS: (ESI-TOF, m/z) calcd. For $C_9H_{11}KN_3O_2$ $[M+K]^+$ calc.: 232.0483; found: 232.0474.

IR: (ATR, neat, cm^{-1}) 2945 (w), 1771 (m), 1697 (s), 1459 (s), 1435 (s), 1385 (m), 1197 (s), 1175 (m), 909 (m), 851 (m), 769 (s), 727 (s), 697 (s), 645 (w), 554 (s).

m.p.: 105 – 106 ºC.



7

Synthesis of 7: The reaction was conducted following the general procedure, except the acetic acid was added with methanol (4.0 mL), and the reaction was then slowly warmed up to rt. The title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 4:1) as a light yellow solid (94.0 mg, 45%).

R_f = 0.24 (SiO_2, hexanes:EtOAc = 2:1, UV, $KMnO_4$).

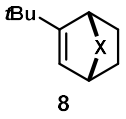
^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.96 (dd, *J* = 5.8, 1.8 Hz, 1H), 4.77 – 4.68 (m, 1H), 4.60 (ddd, *J* = 3.8, 2.1, 1.7 Hz, 1H), 2.96 (s, 3H), 2.07 – 2.09 (m, 2H), 1.84 (d, *J* = 1.7 Hz, 3H), 1.54 – 1.43 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.3, 158.2, 140.4, 122.3, 54.6, 51.1, 25.4, 23.2, 21.7, 19.5.

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{13}N_3NaO_2$ $[M+Na]^+$ calc.: 230.0900; found: 230.0904.

IR: (ATR, neat, cm^{-1}) 2947 (w), 1770 (m), 1694 (s), 1456 (s), 1392 (m), 1208 (s), 1022 (w), 712 (s), 876 (m), 334 (s), 511 (m).

m.p.: 117 – 119 ºC



8

Synthesis of 8: Following the general procedure, the title compound was isolated by flash chromatography (SiO2, hexanes:EtOAc = 4:1) as a light yellow solid (192.0 mg, 77%).

R_f = 0.60 (SiO_2, hexanes:EtOAc = 1:1, UV, $KMnO_4$).

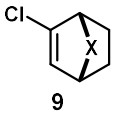
^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.99 (dd, *J* = 5.9, 2.5 Hz, 1H), 4.92 (dt, *J* = 2.5, 2.5 Hz, 1H), 4.81 (dt, *J* = 5.9, 3.0 Hz, 1H), 2.97 (s, 3H), 2.19 (ddt, *J* = 12.5, 9.4, 2.5 Hz, 1H), 2.11 (ddt, *J* = 12.5, 9.4, 3.0 Hz, 1H), 1.53 (tt, *J* = 12.1, 3.0 Hz, 1H), 1.43 (tt, *J* = 12.1, 2.5 Hz, 1H), 1.04 (s, 9H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.6, 156.7, 153.1, 119.0, 51.0, 50.4, 33.4, 28.0, 25.3, 23.4, 23.2.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{20}N_3O_2$ $[M+H]^+$ calc.: 250.1556; found: 250.1548.

IR: (ATR, neat, cm^{-1}) 2968 (w), 1769 (m), 1699 (s), 1630 (w), 1462 (m), 1396 (m), 1366 (m), 1216 (m), 1165 (w), 1024 (w), 923 (w), 856 (w), 764 (m), 697 (w), 573 (w)

m.p.: 107 – 108 ºC



Synthesis of 9: Following the general procedure using dichloromethane instead of ethyl acetate as solvent, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 4:1) as a light yellow solid (94.5 mg, 42%).

R_f = 0.39 (SiO_2, hexanes:EtOAc = 2:1, UV, $KMnO_4$).

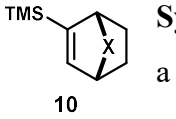
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 6.2, 2.2 Hz, 1H), 4.88 (dt, *J* = 5.9, 2.8 Hz, 1H), 4.84 – 4.82 (m, 1H), 2.99 (s, 3H), 2.22 – 2.09 (m, 2H), 1.75 (m, 1H), 1.58 (m, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.7, 157.4, 131.8, 124.6, 56.8, 51.7, 25.3, 22.6, 22.3.

HRMS: (ESI-TOF, m/z) calcd. For $C_9H_{10}N_3O_2Cl$ $[M]^+$ calc.: 227.0462; found: 227.0467.

IR: (ATR, neat, cm^{-1}) 3076 (w), 2943 (w), 1768 (m), 1714 (s), 1610 (m), 1444 (s), 1013 (m), 849 (m), 766 (s), 533 (m), 521 (m).

m.p.: 110 – 111 ºC.



Synthesis of 10: Following the general procedure, the title compound was isolated as a mixture with **10'** by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a light yellow solid (184.0 mg, 69%, **10:10'** = 1.3:1). The isomers were further separated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) for analytical purposes.

R_f = 0.50 (SiO_2, hexanes:EtOAc = 1:1, UV, $KMnO_4$).

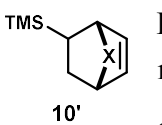
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.57 (dd, *J* = 5.5, 1.4 Hz, 1H), 4.83 (td, *J* = 2.9, 1.4 Hz, 1H), 4.78 (dt, *J* = 5.5, 2.8 Hz, 1H), 2.97 (s, 3H), 2.24 – 2.04 (m, 2H), 1.60 – 1.45 (m, 1H), 1.44 – 1.31 (m, 1H), 0.09 (s, 9H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.2, 157.8, 146.0, 137.1, 52.4, 50.4, 25.4, 22.1, 22.0, –2.5.

HRMS: (ESI-TOF, m/z) calcd. For $C_{12}H_{19}N_3O_2Si$ $[M]^+$ calc.: 265.1247; found: 265.1243.

IR: (ATR, neat, cm^{-1}) 2953 (w), 1706 (s), 1451 (s), 1388 (m), 1262 (m), 1202 (s), 1037 (m), 871 (m), 831 (s), 809 (m), 768 (m), 753 (s), 603 (m), 563 (m), 498 (m).

m.p.: 76 – 78 ºC.



R_f = 0.40 (SiO_2, hexanes:EtOAc = 1:1, UV, $KMnO_4$).

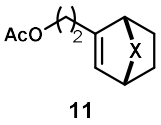
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.48 (ddd, *J* = 8.1, 5.7, 1.5 Hz, 1H), 6.33 (ddd, *J* = 8.1, 5.7, 1.5 Hz, 1H), 4.84 (ddd, *J* = 5.7, 2.8, 1.5 Hz, 1H), 4.77 (ddd, *J* = 5.7, 1.7, 1.6 Hz, 1H), 2.96 (s, 3H), 2.04 (ddd, *J* = 13.0, 5.0, 1.7 Hz, 1H), 1.63 (ddd, *J* = 13.0, 11.8, 2.8 Hz, 1H), 0.83 (ddd, *J* = 11.8, 5.0, 1.6 Hz, 1H), 0.09 (s, 9H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.3, 157.9, 132.5, 128.5, 51.4, 50.8, 25.4, 24.4, 21.5, –2.6.

HRMS: (ESI-TOF, m/z) calcd. For $C_{12}H_{19}N_3O_2Si$ $[M]^+$ calc.: 265.1247; found: 265.1250.

IR: (ATR, neat, cm^{-1}) 2952 (w), 1766 (m), 1698 (s), 1454 (m), 1393 (m), 1249 (m), 1212 (m), 885 (m), 831 (s), 766 (s), 753 (s), 709 (m), 685 (s), 529 (m).

m.p.: 77 – 80 ºC.



11

Synthesis of 11: Following the general procedure the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a light yellow solid (165.9 mg, 59%).

Gram-scale synthesis of 11: MTAD (2.00 g, 17.7 mmol, 1.0 eq.) was placed in a 500 mL borosilicate bottle. Ethyl acetate (150 mL, 0.12 M) was added to the test tube at – 78 ºC, followed by the addition of phenethyl acetate (28.1 mL, 176.9 mmol, 10 eq.). The mixture was then stirred under irradiation with LED lights at –78 ºC until full decolorization of the reaction mixture was observed (pink to colorless solution). The lights were turned off and potassium azodicarboxylate (10.3 g, 53.1 mmol, 3.0 eq.) was added in one portion at –78 ºC, followed by the addition of acetic acid (15.2 mL, 265.3 mmol, 15 eq.) in ethyl acetate (30.0 mL) over 20 minutes. After stirring the resulting suspension at –50 ºC for 12 h, the reaction was warmed up to rt in water bath, then slowly quenched with water (50 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 200 mL). The combined organic layer was washed with saturated aqueous sodium chloride solution (200 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The product was purified by column chromatography (SiO_2, hexanes/EtOAc = 2:1) to yield the desired product **11** (3.36 g, 68%).

R_f = 0.17 (SiO_2, hexanes:EtOAc = 1:1, UV, $KMnO_4$).

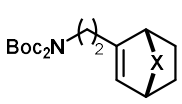
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.12 (d, *J* = 5.6 Hz, 1H), 4.85 (dt, *J* = 5.6, 2.5 Hz, 1H), 4.77 (dt, *J* = 2.3, 2,3 Hz, 1H), 4.28 (dt, *J* = 11.1, 6.1 Hz, 1H), 4.12 (ddd, *J* = 11.1, 7.7, 5.8 Hz, 1H), 3.04 (s, 3H), 2.59 – 2.44 (m, 2H), 2.24 – 2.14 (m, 2H), 2.06 (s, 3H), 1.63 – 1.54 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 170.6, 158.0, 157.8, 140.4, 124.3, 61.5, 53.4, 50.7, 32.4, 25.2, 22.7, 21.9, 20.8.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{18}N_3O_4$ $[M+H]^+$ calc.: 280.1297; found: 280.1293.

IR: (ATR, neat, cm^{-1}) 2954 (w), 1738 (s), 1702 (s), 1464 (m), 1450 (m), 1386 (m), 1250 (s), 1220 (s), 1182 (m), 1028 (m), 963 (m), 857 (w), 764 (w), 530 (w), 460 (w).

m.p.: 66 – 68 ºC



12

Synthesis of 12: Following the general procedure, using dichloromethane instead of ethyl acetate as solvent and 3 eq. of starting arene, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a white solid (165 mg, 45%).

R_f = 0.09 (SiO_2, hexanes:EtOAc = 2:1, UV, $KMnO_4$).

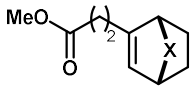
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.1 Hz, 2H), 6.06 (ddd, *J* = 5.9, 1.6 Hz, 1H), 4.78 – 4.73 (m, 2H), 3.84 (ddd, *J* = 13.7, 8.2, 7.1 Hz, 1H), 3.67 (ddd, *J* = 13.7, 8.2, 5.7 Hz, 1H), 2.97 (s, 3H), 2.62 – 2.46 (m, 2H), 2.17 – 2.05 (m, 2H), 1.68 – 1.58 (m, 1H), 1.45 (ddd, *J* = 11.9, 9.1, 2.6 Hz, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 168.1, 158.1, 157.9, 140.8, 134.2, 132.0, 124.2, 123.4, 53.7, 50.9, 35.8, 32.1, 25.5, 22.9, 22.1.

HRMS: (ESI-TOF, m/z) calcd. For $C_{19}H_{18}N_4O_4$ $[M]^+$ calc.: 366.1328; found: 366.1329.

IR: (ATR, neat, cm^{-1}) 2944 (w), 1770 (m), 1702 (s), 1398 (m), 1199 (m), 1010 (m), 769 (m), 723 (s), 531 (m).

m.p.: 186 – 188 ºC



13

Synthesis of 13: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a yellow oil (196.2 mg, 67%).

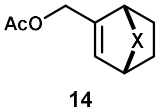
R_f = 0.17 (SiO_2, hexanes:EtOAc = 2:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.00 (dd, *J* = 5.5, 1.7 Hz, 1H), 4.80 (dt, *J* = 5.5, 2.6 Hz, 1H), 4.70 – 4.65 (m, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.99 (s, 3H), 2.52 – 2.32 (m, 4H), 2.19 – 2.07 (m, 2H), 1.62 – 1.47 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 172.3, 158.3, 158.2, 143.0, 122.4, 60.8, 53.8, 50.9, 31.6, 28.3, 25.5, 23.1, 22.1, 14.4.

HRMS: (ESI-TOF, m/z) calcd. For $C_{14}H_{19}KN_3O_4$ $[M+K]^+$ calc.: 332.1007; found: 332.0997.

IR: (ATR, neat, cm^{-1}) 2942 (w), 1701 (s), 1698 (s), 1449 (s), 1393 (m), 1191 (m), 1175 (m), 1162 (m), 1044 (m), 1021 (m), 918 (w), 854 (w), 767 (s), 581 (w), 547 (m).



14

Synthesis of 14: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 1:1) as a light yellow solid (160.2 mg, 60%).

R_f = 0.40 (SiO_2, hexanes:EtOAc = 1:2, UV, $KMnO_4$).

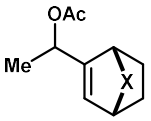
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.28 (ddd, *J* = 5.9, 1.6 Hz, 1H), 4.86 (ddt, *J* = 5.9, 3.0, 1.2 Hz, 1H), 4.80 (dd, *J* = 1.6 Hz, 1H), 4.66 (dd, *J* = 13.6, 1.6 Hz, 1H), 4.55 (dd, *J* = 13.6, 1.5 Hz, 1H), 2.99 (s, 3H), 2.18 (t, *J* = 2.6 Hz, 1H), 2.17 – 2.14 (m, 1H), 2.09 (s, 3H), 1.59 – 1.52 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 170.6, 158.2, 158.0, 138.8, 125.4, 62.7, 51.4, 50.5, 25.3, 22.6, 22.1, 20.8.

HRMS: (ESI-TOF, m/z) calcd. For $C_{12}H_{15}N_3O_4$ $[M]^+$ calc.: 265.1063; found: 265.1060.

IR: (ATR, neat, cm^{-1}) 2944 (w), 1740 (m), 1699 (s), 1451 (m), 1393 (w), 1218 (s), 1027 (m), 912 (m), 767 (m), 729 (s).

m.p.: 57 – 58 ºC



15

Synthesis of 15: Following the general procedure using racemic 1-phenylethyl acetate, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a light yellow solid (162.4 mg, 58%, *dr* = 1.7:1).

R_f = 0.24 (SiO_2, hexanes:EtOAc = 1:1, UV, $KMnO_4$).

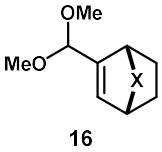
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.15 (m, 1H major, 1H minor), 5.28 (qd, *J* = 6.6, 1.3 Hz, 1H major), 5.15 (qd, *J* = 6.8, 1.2 Hz, 1H minor), 4.83 – 4.69 (m, 2H major, 2 H minor), 2.91 (s, 3H major), 2.87 (s, 3H minor), 2.21 – 2.00 (m, 2H major, 2H minor), 1.98 (d, *J* = 0.9 Hz, 3H major, 3H minor), 1.57 – 1.31 (m, 2H major, 2H minor), 1.24 (dd, *J* = 6.7, 0.9 Hz, 3H major, 3H minor).

^{13}C NMR: (126 MHz, CDCl3) δ 170.1 (major), 170.1 (minor), 158.1 (minor), 158.0 (major), 157.7 (minor), 157.5 (major), 143.4 (minor), 143.0 (major), 123.4 (major), 123.4 (minor), 69.1 (minor), 68.4 (major), 50.8 (major), 50.6 (minor), 50.3 (minor), 50.2 (major), 25.2 (major), 25.1 (minor), 22.8 (minor), 22.5 (major), 22.5 (minor), 22.4 (major), 21.1 (minor), 20.9 (major), 19.1 (minor), 18.3 (major).

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{17}N_3O_4$ $[M+H]^+$ calc.: 279.1219; found: 279.1218.

IR: (ATR, neat, cm^{-1}) 2968 (w), 1769 (m), 1699 (s), 1630 (w), 1462 (m), 1396 (m), 1366 (m), 1216 (m), 1165 (w), 1024 (w), 923 (w), 856 (w), 764 (m), 697 (w), 573 (w).

m.p.: 86 – 88 ºC



16

Synthesis of 16: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a yellow oil (128.1 mg, 48%).

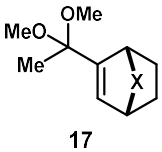
R_f = 0.14 (SiO_2, hexanes:EtOAc = 1:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.31 (dt, *J* = 5.9, 1.6 Hz, 1H), 4.84 – 4.82 (m, 2H), 4.70 (d, *J* = 1.4 Hz, 1H), 3.24 (s, 3H), 3.17 (s, 3H), 2.91 (s, 3H), 2.12 – 2.07 (m, 2H), 1.53 – 1.47 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.9, 157.5, 140.5, 125.9, 101.5, 54.2, 53.2, 50.5, 50.4, 25.5, 22.9, 22.5.

HRMS: (ESI-TOF, m/z) calcd. For $C_{12}H_{17}N_3O_4Na$ $[M+Na]^+$ calc.: 290.1117; found: 290.1113.

IR: (ATR, neat, cm^{-1}) 2942 (w), 2832 (w), 1774 (m), 1699 (s), 1447 (m), 1392 (m), 1193 (m), 1018 (m), 1053 (m), 909 (w), 766 (m), 547 (m).



17

Synthesis of 17: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a light yellow oil (164.0 mg, 58%).

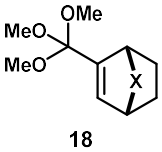
R_f = 0.24 (SiO_2, hexanes:EtOAc = 1:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.43 (dd, *J* = 5.4, 1.9 Hz, 1H), 4.99 (d, *J* = 2.4 Hz, 1H), 4.92 (dt, *J* = 5.4, 2.2 Hz, 1H), 3.14 (s, 3H), 3.12 (s, 3H), 2.99 (s, 3H), 2.23 – 2.13 (m, 2H), 1.60 – 1.54 (m, 2H), 1.37 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.4, 156.9, 144.4, 125.5, 99.5, 50.6, 50.1, 49.3, 49.1, 25.4, 23.0, 22.8, 22.6.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{23}N_4O_4$ $[M+NH_4]^+$ calc.: 299.1714; found: 299.1716.

IR: (ATR, neat, cm^{-1}) 2944 (w), 1767 (m), 1699 (s), 1449 (s), 1393 (s), 1188 (s), 1143 (s), 1106 (m), 1033 (s), 873 (m), 856 (m), 765 (s), 696 (m), 557 (m).



18

Synthesis of 18: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a light yellow oil (159.3 mg, 54%).

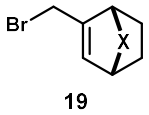
R_f = 0.14 (SiO_2, hexanes:EtOAc = 1:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.52 (dd, *J* = 5.9, 1.8 Hz, 1H), 4.97 (dd, *J* = 2.2 Hz, 1H), 4.90 (dt, *J* = 5.9, 2.4 Hz, 1H), 3.08 (s, 9H), 2.93 (s, 3H), 2.13 (m, 2H), 1.56 – 1.50 (m, 2H).

^{13}C NMR: (126 MHz, CDCl3) δ 156.6, 155.9, 138.6, 129.3, 112.7, 50.0, 49.9, 49.4, 25.3, 23.1, 22.6.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{19}N_3O_5Na$ $[M+Na]^+$ calc.: 320.1220; found: 320.1222.

IR: (ATR, neat, cm^{-1}): 2947 (w), 1772 (w), 1709 (s), 1446 (m), 1394 (m), 1211 (m), 1086 (s), 1068 (s), 920 (w), 871 (w), 763 (m), 543 (w).



19

Synthesis of 19: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a light yellow solid (183.0 mg, 64%).

R_f = 0.27 (SiO_2, hexanes:EtOAc = 2:1, UV, $KMnO_4$).

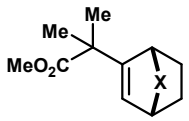
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.30 (dt, *J* = 6.1, 1.6 Hz, 1H), 4.83 (m, 2H), 3.99 (dd, *J* = 10.8, 1.6 Hz, 1H), 3.90 (dd, *J* = 10.8, 0.8 Hz, 1H), 2.95 (s, 3H), 2.22 – 2.14 (m, 2H), 1.66 – 1.54 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.9, 157.7, 139.5, 126.0, 53.1, 50.9, 30.5, 25.4, 22.9, 22.8.

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{12}N_3O_2Br$ $[M]^+$ calc.: 285.0113; found: 285.0112.

IR: (ATR, neat, cm^{-1}) 2944 (w), 2249 (w), 1771 (m), 1695 (s), 1450 (s), 1392 (m), 1202 (m), 1016 (w), 912 (m), 765 (m), 728 (m).

m.p.: 108 – 110 ºC.



20

Synthesis of 20: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a colorless oil (194.2 mg, 66%).

R_f = 0.45 (SiO_2, hexanes:EtOAc = 1:2, UV, $KMnO_4$).

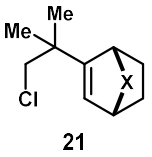
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 6.0, 2.1 Hz, 1H), 4.89 – 4.86 (m, 2H), 3.67 (s, 3H), 2.98 (s, 3H), 2.21 – 2.09 (m, 2H), 1.64 – 1.51 (m, 2H), 1.34 (s, 3H), 1.32 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 175.0, 157.3, 156.5, 146.8, 122.3, 52.4, 51.7, 50.1, 45.0, 25.2, 24.3, 23.4, 23.1, 22.9.

HRMS: (ESI-TOF, m/z) calcd. For $C_{14}H_{19}N_3O_4$ $[M+H]^+$ calc.: 294.1446; found: 294.1454.

IR: (ATR, neat, cm^{-1}): 2946 (w), 1769 (m), 1696 (s), 1450 (m), 1392 (m), 1210 (m), 1019 (w), 913 (m), 727 (s), 571 (m).

m.p.: 105 ºC



21

Synthesis of 21: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a light yellow solid (190.0 mg, 67%).

R_f = 0.55 (SiO_2, hexanes:EtOAc = 1:2, UV, $KMnO_4$).

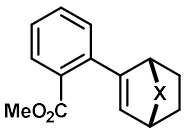
^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.14 (dd, *J* = 6.0, 2.1 Hz, 1H), 4.89 – 4.83 (m, 2H), 3.51 (d, *J* = 11.1 Hz, 1H), 3.42 (d, *J* = 11.1 Hz, 1H), 2.97 (s, 3H), 2.25 – 2.06 (m, 2H), 1.64 – 1.48 (m, 2H), 1.15 (s, 3H), 1.14 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.7, 157.2, 147.2, 123.5, 52.3, 50.4, 50.3, 38.4, 25.2, 24.0, 23.8, 23.1, 22.6.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{18}N_3O_2Cl$ $[M]^+$ calc.: 283.1088; found: 283.1088.

IR: (ATR, neat, cm^{-1}) 2946 (w), 1769 (m), 1696 (s), 1450 (m), 1392 (m), 1210 (m), 1019 (w), 913 (m), 830 (m), 727 (s), 571 (m).

m.p.: 97 – 98 ºC.



22

Synthesis of 22: Following the general procedure, the title compound was isolated as a mixture with **22'** by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a colorless oil (215.0 mg, 66%, **22:22'** = 1.9:1). The constitutional isomers were further separated by flash chromatography (SiO2, hexanes:EtOAc = 2:1).

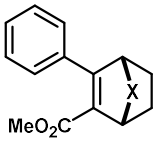
R_f = 0.21 (SiO_2, hexanes:EtOAc = 2:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.49 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.36 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.28 – 7.25 (m, 1H), 6.20 (dd, *J* = 6.0, 1.9 Hz, 1H), 5.00 (dt, *J* = 4.4, 2.2 Hz, 1H), 4.93 (dd, *J* = 5.7, 2.7 Hz, 1H), 3.81 (s, 3H), 3.02 (s, 3H), 2.26 – 2.20 (m, 2H), 2.07 – 2.01 (m, 1H), 1.69 (ddd, *J* = 10.6, 6.0, 3.1 Hz, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 168.3, 158.2, 157.9, 142.8, 137.2, 132.0, 130.3, 130.1, 129.3, 128.3, 125.5, 55.0, 52.3, 51.0, 25.5, 22.7, 22.4.

HRMS: (ESI-TOF, m/z) calcd. For $C_{17}H_{17}N_3O_4Na$ $[M+Na]^+$ calc.: 350.1117; found: 350.1111.

IR: (ATR, neat, cm^{-1}) 2949 (w), 2252 (w), 1772 (m), 1699 (s), 1447 (m), 1393 (m), 1269 (m), 911 (m), 756 (m), 727 (m), 545 (w).



22'

The titled compound was isolated as a colorless oil.

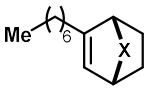
R_f = 0.25 (SiO_2, hexanes:EtOAc = 2:1, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 5H), 5.47 (t, *J* = 2.8 Hz, 1H), 5.08 (t, *J* = 2.8 Hz, 1H), 3.65 (s, 3H), 3.03 (s, 3H), 2.33 – 2.24 (m, 2H), 1.81 – 1.64 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 164.0, 157.7, 157.5, 150.6, 134.3, 129.5, 128.4, 128.4, 125.7, 56.4, 52.2, 51.6, 25.7, 22.6, 21.9.

HRMS: (ESI-TOF, m/z) calcd. For $C_{17}H_{17}N_3O_4Na$ $[M+Na]^+$ calc.: 350.1117; found: 350.1110.

IR: (ATR, neat, cm^{-1}) 2950 (w), 2254 (w), 1770 (m), 1703 (s), 1446 (m), 1393 (m), 1225 (m), 916 (m), 768 (m), 698 (m), 577 (m).



23

Synthesis of 23: Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 4:1) as a light yellow solid (150.3 mg, 52%).

R_f = 0.70 (SiO_2, hexanes:EtOAc = 1:1, UV, $KMnO_4$).

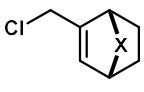
^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.95 (dd, *J* = 5.6, 1.7 Hz, 1H), 4.77 (dd, *J* = 5.6, 2.6 Hz, 1H), 4.64 (dd, *J* = 2.6 Hz, 1H), 2.97 (s, 3H), 2.18 – 2.03 (m, 4H), 1.54 – 1.48 (m, 2H), 1.44 – 1.33 (m, 2H), 1.32 – 1.14 (m, 8H), 0.86 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.2, 157.9, 144.7, 121.6, 53.9, 51.0, 33.4, 31.9, 29.13, 29.07, 26.7, 25.4, 23.2, 22.7, 22.3, 14.2.

HRMS: (ESI-TOF, m/z) calcd. For $C_{16}H_{25}N_3NaO_2$ $[M+Na]^+$ calc.: 314.1839; found: 314.1830.

IR: (ATR, neat, cm^{-1}) 2926 (m), 2855 (w), 1772 (m), 1701 (s), 1451 (s), 1393 (m), 1203 (m), 1013 (m), 912 (w), 766 (m).

m.p.: 40 – 42 ºC



24

Synthesis of 24: Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a light yellow solid (150.3 mg, 66%).

R_f = 0.41 (SiO_2, hexanes:EtOAc = 1:2, UV, $KMnO_4$)

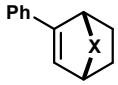
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (dd, *J* = 5.7, 1.4 Hz, 1H), 4.87 – 4.84 (m, 2H), 4.12 (dd, *J* = 12.5, 1.4 Hz, 1H), 4.04 (dd, *J* = 12.5, 1.1 Hz, 1H), 2.97 (s, 3H), 2.25 – 2.09 (m, 2H), 1.71 – 1.44 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 157.8, 139.54, 125.8, 52.4, 50.8, 43.5, 25.5, 22.8, 22.7.

IR (ATR, neat, cm^{-1}): 2946 (w), 1772 (w), 1695 (s), 1450 (s), 1392 (m), 1202 (m), 1017 (m), 766 (m), 698 (m), 543 (w).

HRMS (ESI-TOF, m/z) calcd. For $C_{10}H_{12}ClN_3O_2$ $[M]^+$ calc.: 241.0613; found: 241.0619.

m.p.: 104.7-105.6 °C



25

Synthesis of 25: Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a light yellow solid (120.3 mg, 23%).

R_f = 0.61 (SiO_2, *n*-hexane/EtOAc = 1:2, $KMnO_4$)

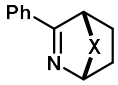
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 2H), 7.46 – 7.40 (m, 2H), 7.40 – 7.35 (m, 1H), 6.56 (dd, *J* = 5.9, 2.1 Hz, 1H), 5.04 (dt, *J* = 5.6, 2.6 Hz, 1H), 3.00 (s, 3H), 2.34 – 2.26 (m, 2H), 1.69 (dt, *J* = 9.6, 2.1 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 158.1, 142.9, 134.8, 129.1, 128.8, 125.6, 122.1, 52.6, 51.0, 25.5, 22.5, 22.3.

IR (ATR, neat, cm^{-1}): 2942 (w), 1771 (m), 1698 (s), 1446 (s), 1392 (m), 1203 (m), 1018 (w), 911 (m), 770 (s), 754 (s) 730 (m), 695 (m), 551 (m).

HRMS (EI-TOF, m/z) calcd. For $C_{15}H_{15}N_3O_2$ $[M+H]^+$ calc.: 269.1164; found: 269.1164.

MP: 142.9 - 144.0 °C



26

Synthesis of 26: Following the general procedure A, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a light yellow solid (142.4 mg, 34%).

R_f = 0.55 (SiO_2, *n*-hexane:EtOAc = 1:2, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.81 (m, 2H), 7.56 – 7.49 (m, 1H), 7.50 – 7.43 (m, 2H), 6.15 (t, *J* = 2.5 Hz, 1H), 5.39 (t, *J* = 2.8 Hz, 1H), 2.96 (s, 3H), 2.33 (ddt, *J* = 12.4, 9.6, 2.6 Hz, 1H), 2.27 (ddt, *J* = 12.4, 9.6, 2.6 Hz, 1H), 1.73 (tt, *J* = 12.4, 2.9 Hz, 1H), 1.65 (tt, *J* = 12.4, 2.9 Hz, 1H).

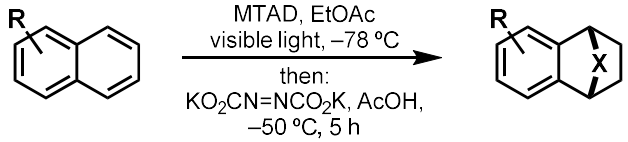
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 157.9, 157.5, 133.3, 132.1, 129.1, 126.9, 67.1, 48.8, 25.6, 21.4, 20.0.

IR (ATR, neat, cm^{-1}): 2946 (w), 1776 (m), 1702 (s), 1595 (m), 1568 (m), 1446 (s), 1392 (m), 1364 (m), 1194 (m), 1060 (m), 1025 (m), 1013 (m), 916 (m), 793 (m), 764 (m), 718 (s), 690 (m), 645 (m), 576 (m), 555 (m).

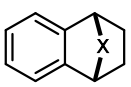
HRMS (EI-TOF, m/z) calcd. For $C_{14}H_{15}N_4O_2$ $[M+H]^+$ calc.: 271.1186; found: 271.1195.

MP: 162.4 – 163.5 °C

Polynuclear arene cycloaddition



MTAD (**1**, 113.1 mg, 1.0 mmol, 1.0 eq.) was placed in a test tube. Ethyl acetate (10 mL, 0.1 M) was added to the test tube at –78 ºC, followed by the addition of arene (2.0 mmol, 2.0 eq.). If arene was a solid, ethyl acetate (5.0 mL) was added to MTAD at –78 ºC, and arene was added as a solution in ethyl acetate (5.0 mL). The mixture was then stirred under the irradiation with LED lights at –78 ºC until full decolorization of the reaction mixture was observed (pink to colorless solution). At –78 ºC, potassium azodicarboxylate (582.7 mg, 3.0 mmol, 3.0 eq.) was added in one portion, followed by the addition of acetic acid (0.86 mL, 15 mmol, 15 eq.) in ethyl acetate (4.0 mL). After stirring the resulting suspension at –50 ºC for 5 h, the reaction was warmed up to rt in water bath, then quenched with water (2.0 mL). Saturated aqueous sodium bicarbonate solution (7.5 mL) was added, and then the organic phase was separated. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with saturated aqueous sodium chloride solution (15 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc mixture) to provide cycloadduct.



28

Synthesis of 28: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 1:1) as a white solid (212.1 mg, 87%).

Synthesis of 28 on gram-scale: Naphthalene (2.56 g, 20.0 mmol, 2.0 eq.) and MTAD (1.13 g, 10.0 mmol, 1.0 eq.) were placed in a 500 mL borosilicate bottle, and ethyl acetate (100 mL, 0.10 M) was added at –78 ºC. The mixture was then stirred under irradiation with LED lights

at –78 ºC until full decolorization of the reaction mixture was observed (pink to colorless solution). The lights were turned off and potassium azodicarboxylate (5.83 g, 30.0 mmol, 3.0 eq.) was added in one portion at –78 ºC, followed by the addition of acetic acid (8.85mL, 150 mmol, 15 eq.) in ethyl acetate (20.0 mL) over 15 minutes. The resulting suspension was immediately placed out of the cold bath and stirred at ambient temperature for 5 hours. Water (50 mL) was added and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 100 mL) and the combined organic layer was washed with saturated aqueous sodium chloride solution (100 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The product was purified by column chromatography (SiO_2, hexanes/EtOAc = 5:1 → 1:1). The obtained pale yellow solid was recrystallized from diethylether/hexanes to yield the desired product **28** (2.00 g, 82%).

R_f = 0.35 (SiO_2, hexanes:EtOAc = 1:2, UV, $KMnO_4$).

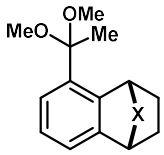
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 5.4, 3.3 Hz, 2H), 7.29 (dd, *J* = 5.4, 3.3 Hz, 2H), 5.30 – 5.28 (m, 2H), 2.84 (s, 3H), 2.42 – 2.36 (m, 2H), 1.73 – 1.68 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.9, 134.9, 128.8, 123.4, 53.8, 25.2, 23.5.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{13}N_3O_2$ [M]+ calc.: 243.1007; found: 243.1008.

IR: (ATR, neat, cm^{-1}) 2942 (w), 1764 (m), 1698 (s), 1458 (s), 1436 (s), 1395 (s), 1237 (m), 1204 (s), 1165 (m), 1069 (w), 1037 (m), 988 (m), 946 (m), 915 (m), 753 (s), 593 (m), 538 (s).

m.p.: 190 – 191 ºC.



29

Synthesis of 29: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1, 1% Et_3N) as a white solid (220.0 mg, 66%).

R_f = 0.57 (SiO_2, hexanes:EtOAc = 1:2, UV, $KMnO_4$).

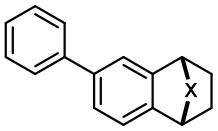
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.30 (dd, *J* = 8.1, 7.3 Hz, 1H), 7.21 (dd, *J* = 7.3, 1.3 Hz, 1H), 6.16 (t, *J* = 2.5 Hz, 1H), 5.27 (t, *J* = 2.3 Hz, 1H), 3.25 (s, 3H), 3.23 (s, 3H), 2.87 (s, 3H), 2.37 – 2.34 (m, 2H), 1.73 – 1.68 (m, 2H), 1.67 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.3, 155.6, 138.0, 136.1, 133.5, 128.0, 127.5, 123.4, 102.1, 53.7, 50.5, 49.2, 49.2, 26.0, 25.3, 23.8, 23.4.

HRMS: (ESI-TOF, m/z) calcd. For $C_{17}H_{21}N_3O_4Na$ $[M+Na]^+$ calc.: 354.1430; found: 354.1428.

IR: (ATR, neat, cm^{-1}) 2945 (w), 2249 (w), 1764 (m), 1700 (s), 1453 (m), 1394 (m), 1275 (m), 1206 (m), 1146 (m), 1038 (m), 876 (m), 762 (m), 729 (m), 562 (m).

m.p.: 168 – 169 ºC.



30

Synthesis of 30: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a white solid (136.4 mg, 43%).

R_f = 0.53 (SiO_2, hexanes:EtOAc = 1:2, UV, $KMnO_4$).

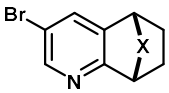
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 3H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.47 – 7.41 (t, *J* = 7.6 Hz, 2H), 7.36 (dt, *J* = 7.6, 3.5 Hz, 2H), 5.37 – 3.33 (m, 2H), 2.86 (s, 3H), 2.45 – 2.41 (m, 2H), 1.77 – 1.73 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.1, 157.1, 142.1, 140.3, 135.6, 133.9, 129.0, 127.9, 127.6, 127.3, 124.0, 122.4, 54.1, 53.7, 25.4, 23.8, 23.8.

HRMS: (ESI-TOF, m/z) calcd. For $C_{19}H_{18}N_3O_2$ $[M+H]^+$ calc.: 320.1399; found: 320.1396.

IR: (ATR, neat, cm^{-1}) 2944 (w), 1763 (m), 1700 (s), 1480 (m), 1453 (m), 1393 (m), 1212 (w), 1027 (w), 916 (w), 760 (m), 730 (m), 699 (m), 535 (w).

m.p.: 234 – 235 ºC.



31

Synthesis of 31: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 1:2) as a yellow solid (284.1 mg, 88%).

R_f = 0.39 (SiO_2, hexanes:EtOAc = 1:4, UV, $KMnO_4$).

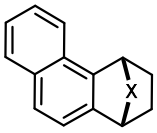
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 2.1 Hz, 1H), 7.77 (d, *J* = 2.1 Hz, 1H), 5.43 (t, *J* = 2.7 Hz, 1H), 5.33 (t, *J* = 2.7 Hz, 1H), 2.88 (s, 3H), 2.52 – 2.35 (m, 2H), 1.85 – 1.74 (m, 1H), 1.75 – 1.63 (m, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.8, 156.5, 153.0, 150.8, 133.9, 131.0, 121.0, 55.1, 52.9, 25.6, 23.4, 22.7.

HRMS: (ESI-TOF, m/z) calcd. For $C_{12}H_{11}BrN_4O_2$ $[M]^+$ calc.: 322.0060; found: 322.0063.

IR: (ATR, neat, cm^{-1}) 2946 (w), 1765 (w), 1702 (s), 1448 (m), 1392 (m), 1214 (w), 986 (w), 764 (w), 729 (w), 629 (w).

m.p.: 165– 166 ºC.



32

Synthesis of 32: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 2:1) as a white solid (150.9 mg, 51%).

R_f = 0.54 (SiO_2, hexanes:EtOAc = 1:2, UV, $KMnO_4$).

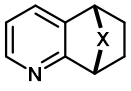
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.62 (ddt, *J* = 8.2, 6.8, 1.1 Hz, 1H), 7.54 (ddt, *J* = 8.2, 6.8, 1.1 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 6.09 (t, *J* = 2.7 Hz, 1H), 5.45 (t, *J* = 2.7 Hz, 1H), 2.77 (s, 3H), 2.59 – 2.42 (m, 2H), 1.79 – 1.65 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.5, 157.3, 133.4, 132.4, 131.0, 128.8, 128.7, 127.7, 127.4, 126.3, 122.1, 121.5, 54.3, 49.4, 25.2, 23.7, 23.2.

HRMS: (ESI-TOF, m/z) calcd. For $C_{17}H_{16}N_3O_2$ $[M+H]^+$ calc.: 294.1243; found: 294.1242.

IR: (ATR, neat, cm^{-1}) 2943 (w), 2250 (w), 1767 (m), 1699 (s), 1451 (s), 1393 (s), 1207 (m), 1024 (m), 914 (m), 819 (m), 765 (m), 728 (s), 595 (m).

m.p.: 167 – 168 ºC.



33

Synthesis of 33: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 1:4) as a white solid (250.9 mg, 92%).

R_f = 0.10 (SiO_2, *n*-hexane:EtOAc = 1:2, $KMnO_4$)

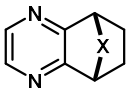
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 5.1, 1.6 Hz, 1H), 7.65 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.34 (dd, *J* = 7.6, 5.1 Hz, 1H), 5.50 (t, *J* = 2.8 Hz, 1H), 5.40 (t, *J* = 2.8 Hz, 1H), 2.91 (s, 3H), 2.55 – 2.41 (m, 2H), 1.91 – 1.82 (m, 1H), 1.79 – 1.70 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.8, 156.5, 154.6, 149.7, 131.2, 129.8, 124.1, 55.6, 53.2, 25.4, 23.5, 22.8.

HRMS (EI-TOF, m/z) calcd. For $C_{12}H_{13}N_4O_2$ $[M+H]^+$ calc.: 245.1033; found: 245.1039.

IR (ATR, neat, cm^{-1}): 2946 (w), 1769 (m), 1700 (s), 1581 (w), 1455 (s), 1394 (m), 1217 (m), 1029 (w), 983 (w), 800 (w), 762 (m), 594 (w), 544 (w).

MP: 158.8 - 159.6 °C



34

Synthesis of 34: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 1:4 to EtOAc) as a yellow solid (201.3 mg, 82%).

R_f = 0.14 (SiO2, hexanes:EtOAc = 1:4, UV, KMnO4).

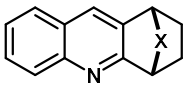
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.46 (s, 2H), 5.49 – 5.46 (m, 2H), 2.82 (s, 3H), 2.49 – 2.43 (m, 2H), 1.81 – 1.75 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 155.9, 149.7, 144.7, 54.8, 25.4, 22.8.

HRMS: (ESI-TOF, m/z) calcd. For $C_{11}H_{11}N_5O_2$ $[M]^+$ calc.: 245.0913; found: 245.0913.

IR: (ATR, neat, cm^{-1}) 2948 (w), 1764 (m), 1701 (s), 1454 (m), 1392 (m), 1233 (w), 1207 (w), 1134 (m), 985 (m), 854 (w), 762 (m), 729 (m), 595 (m).

m.p.: 172– 173 ºC.



35

Synthesis of 35: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 1:2) as a brown solid (179.5 mg, 61%).

R_f = 0.33 (SiO_2, hexanes:EtOAc = 1:4, UV, $KMnO_4$).

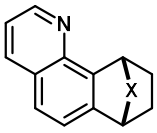
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.13 (dt, *J* = 8.5, 0.9 Hz, 1H), 8.05 (s, 1H), 7.85 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.77 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.9, 0.9 Hz, 1H), 5.56 (t, *J* = 2.8 Hz, 1H), 5.49 (t, *J* = 2.8 Hz, 1H), 2.85 (s, 3H), 2.62 – 2.47 (m, 2H), 2.02 – 1.93 (m, 1H), 1.87 – 1.77 (m, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.7, 156.2, 155.0, 147.8, 130.6, 130.3, 129.8, 128.3, 128.2, 127.7, 127.4, 56.0, 53.4, 25.5, 24.2, 23.1.

HRMS: (ESI-TOF, m/z) calcd. For $C_{16}H_{15}N_4O_2$ $[M+H]^+$ calc.: 295.1190; found: 295.1185.

IR: (ATR, neat, cm^{-1}) 2945 (w), 1699 (s), 1452 (m), 1392 (m), 1209 (w), 1025 (w), 861 (w), 762 (m), 732 (m), 542 (m).

m.p.: 183– 184 ºC.



36

Synthesis of 36: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 1:2) as a yellow solid (157.7 mg, 54%).

$\mathbf{R_f}$ = 0.33 (SiO_2, hexanes:EtOAc = 1:4, UV, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.98 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.42 (dd, *J* = 8.2, 4.2 Hz, 1H), 6.63 (t, *J* = 2.6 Hz, 1H), 5.48 (t, *J* = 2.6 Hz, 1H), 2.75 (s, 3H), 2.54 – 2.42 (m, 2H), 1.76 – 1.67 (m, 2H).

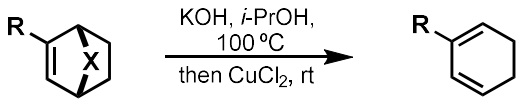
^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.3, 156.9, 151.5, 142.4, 136.4, 135.9, 132.9, 128.4, 128.1, 122.2, 121.7, 53.9, 48.4, 25.3, 23.8, 23.0.

HRMS: (ESI-TOF, m/z) calcd. For $C_{16}H_{14}KN_4O_2$ $[M+K]^+$ calc.: 333.0748; found: 333.0764.

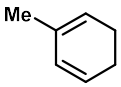
IR: (ATR, neat, cm-1) 2942 (w), 1764 (m), 1698 (s), 1451 (s), 1393 (m), 1209 (m), 1158 (w), 1024 (w), 840 (m), 764 (m).

m.p.: 220– 221 ºC.

Cycloreversion of MTAD cycloadducts



Cycloadduct (0.4 mmol, 1.0 eq.) and potassium hydroxide (248.9 mg, 90% w/w, 4.0 mmol, 10.0 eq.) in 2-propanol (2.0 mL, 0.2 M) were stirred at 100 ºC under a nitrogen atmosphere until full conversion of **3** was observed by TLC analysis. Reaction was then cooled to 0 ºC, and acetic acid 0.23 mL (4.0 mmol, 10.0 eq.) was added dropwise to neutralize to pH 6. Volatiles were then removed *in vacuo*, and the resulting residue was dissolved in distilled water (1.0 mL). An aqueous solution of $CuCl_2$ (1.0 M, 0.4 mL, 1.0 eq.) was added, and the mixture was stirred for one minute. Aqueous ammonium hydroxide (5.0 M, 1.5 mL) was then added to the resulting brown solution, and the color of the solution turned dark blue. After adding ethyl acetate (5 mL), the mixture was transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), dried over magnesium sulfate, and concentrated *in vacuo*. For most of the cases, the desired cyclohexadiene was obtained in analytically pure form without further purification. Otherwise, the crude mixture was purified by flash chromatography (SiO_2, *n*-hexane:EtOAc mixtures).



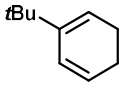
37

Synthesis of 37: Following the general procedure, the title compound was synthesized and confirmed by NMR analysis (yellow oil, 53% yield based on ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.85 – 5.70 (m, 2H), 5.50 – 5.35 (m, 1H), 2.11 – 2.04 (m, 4H), 1.71 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 131.6, 128.3, 126.6, 120.6, 31.7, 22.8, 22.6.

The analytical data was in accordance with previously reported values.[36]



38

Synthesis of 38: Following the general procedure, the title compound was synthesized and confirmed by NMR analysis (yellow oil, 90% yield based on ^{1}H NMR analysis using $MeNO_2$ as an internal standard).

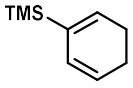
R_f = 0.77 (SiO_2, hexanes:EtOAc = 10:1, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.07 (dd, *J* = 9.7, 1.9 Hz, 1H), 5.86 (dtd, *J* = 9.7, 4.5, 0.9 Hz, 1H), 5.54 (tdd, *J* = 4.5, 1.9, 0.9 Hz, 1H), 2.14 – 2.07 (m, 2H), 2.06 – 1.98 (m, 2H), 1.04 (s, 9H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 144.1, 126.6, 125.2, 116.5, 34.0, 29.0, 22.7, 22.4.

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{16}Na$ $[M+Na]^+$ calc.: 159.1144; found: 159.1147.

IR: (ATR, neat, cm^{-1}) 2955 (w), 2924 (w), 2856 (w), 1717 (w), 1462 (w).



39

Synthesis of 39: Following the general procedure, the title compound was isolated as a colorless oil (48.3 mg, 79%).

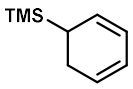
R_f = 0.87 (SiO_2, hexanes:EtOAc = 10:1, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.10 (tt, *J* = 4.3, 1.2 Hz, 1H), 6.01 (ddt, *J* = 9.6, 1.9, 1.2 Hz, 1H), 5.81 (ddt, *J* = 9.6, 4.3, 1.2 Hz, 1H), 2.18 – 2.01 (m, 4H), 0.07 (s, 9H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 136.1, 135.1, 126.4, 125.4, 23.3, 22.0, –1.8.

HRMS: (ESI-TOF, m/z) calcd. For $C_9H_{16}Si$ $[M]^+$ calc.: 152.1016; found: 152.1014.

IR: (ATR, neat, cm^{-1}) 2953 (m), 2925 (m), 2859 (w), 1710 (w), 1679 (w), 1455 (w), 1248 (m), 838 (s), 753 (w).



40

Synthesis of 40: Following the general procedure, the title compound was isolated as a colorless oil (55.3 mg, 91%).

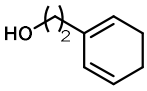
R_f = 0.87 (SiO_2, hexanes:EtOAc = 10:1, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.84 – 5.70 (m, 3H), 5.60 (ddt, *J* = 7.5, 5.1, 3.9, 1.1 Hz, 1H), 2.48 (dddd, *J* = 17.0, 10.2, 3.9, 2.1 Hz, 1H), 2.18 (dddd, *J* = 17.0, 7.8, 5.1, 1.6 Hz, 1H), 1.64 (dddd, *J* = 10.2, 7.8, 4.8, 1.6 Hz, 1H), 0.02 (s, 9H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 129.1, 124.7, 124.5, 122.3, 24.0, 23.2, –2.7.

HRMS: (ESI-TOF, m/z) calcd. For $C_9H_{16}Si$ $[M]^+$ calc.: 152.1016; found: 152.1018.

IR: (ATR, neat, cm^{-1}) 2953 (m), 2923 (m), 1679 (m), 1541 (m), 1462 (m), 1413 (w), 1248 (s), 1104 (w), 836 (s), 752 (m).



41

Synthesis of 41: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 4:1) as a colorless oil (42.3 mg, 85%).

Synthesis of 41 on large scale: Following the general procedure using compound 14 (881.0 mg, 3.15 mmol, 1.0 eq.), the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 4:1) as a colorless oil (300.0 mg, 77%).

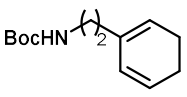
R_f = 0.30 (SiO_2, hexanes:EtOAc = 2:1, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.92 – 5.85 (m, 1H), 5.83 (dd, *J* = 9.7, 1.5 Hz, 1H), 5.60 (tt, *J* = 4.0, 1.5 Hz, 1H), 3.67 (t, *J* = 6.2 Hz, 2H), 2.29 (td, *J* = 6.2, 1.4 Hz, 2H), 2.20 – 2.07 (m, 4H), 1.41 (br, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 133.1, 128.0, 126.7, 123.4, 61.2, 39.1, 22.6, 22.5.

HRMS: (ESI-TOF, m/z) calcd. For $C_8H_{12}O$ $[M]^+$ calc.: 124.0883; found: 124.0880.

IR: (ATR, neat, cm^{-1}): 3338 (br, m), 3033 (w), 2931 (m), 2873 (m), 2822 (m), 1426 (w), 1359 (w), 1046 (s), 736 (m), 589 (m).



42

Synthesis of 42: Compound 12 (100.0 mg, 0.27 mmol, 1.0 eq.) was refluxed in anhydrous hydrazine (0.17 mL, 5.5 mmol, 20 eq.) at 100 ºC for 20 h. Volatiles were removed in vacuo, and the residue was taken up in THF:H_2O (2:1, 1.5 mL). Sodium bicarbonate (114.6 mg, 1.36 mmol, 5.0 eq.) and di-tert-butyl dicarbonate (119.1 mg, 0.55

mmol, 2.0 eq.) were added, and the reaction mixture was stirred at 50 ºC for 2 h. $CuCl_2$ (0.8 mL, 1.0 M in H_2O, 3.0 eq.) was then added at rt, and the mixture was further stirred for one minute. After adding ethyl acetate (5.0 mL), the mixture was transferred to a separatory funnel. The organic layer was separated, and the aqueous later extracted with ethyl acetate (3 × 5.0 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), dried over magnesium sulfate, and concentrated in vacuo. The crude mixture was purified by flash chromatography (SiO2, hexanes:EtOAc mixtures) to provide the desired compound **42** as a colorless oil (42.0 mg, 69%).

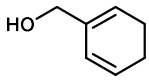
R_f = 0.42 (SiO_2, hexanes:EtOAc = 10:1, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.90 – 5.76 (m, 2H), 5.53 (ddt, *J* = 5.4, 3.7, 1.4 Hz, 1H), 4.52 (s, 1H), 3.21 – 3.17 (m, 2H), 2.20 – 2.17 (m, 2H), 2.13 – 2.09 (m, 4H), 1.44 (s, 9H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.2, 133.1, 127.8, 126.8, 122.7, 79.2, 39.5, 36.2, 28.8, 22.45, 22.41.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{21}NO_2$ $[M]^+$ calc.: 223.1572; found: 223.1568.

IR: (ATR, neat, cm^{-1}) 3355 (w), 2976 (w), 2930 (w), 2873 (w), 1690 (s), 1505 (m), 1365 (m), 1249 (m), 1166 (s), 736 (w).



43

Synthesis of 43: Following the general procedure, the title compound was isolated as a colorless oil (36.9 mg, 84%).

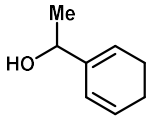
R_f = 0.42 (SiO_2, hexanes:EtOAc = 2:1, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.00 (dd, *J* = 9.8, 1.6 Hz, 1H), 5.97 – 5.88 (m, 1H), 5.77 (tt, *J* = 3.9, 1.6 Hz, 1H), 4.12 (d, *J* = 1.6 Hz, 2H), 2.27 – 2.14 (m, 4H), 1.42 (s, 1H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 135.7, 127.8, 124.6, 122.3, 65.8, 22.4, 22.2.

HRMS: (ESI-TOF, m/z) calcd. For $C_7H_{11}O$ $[M+H]^+$ calc.: 111.0804; found: 111.0809.

IR: (ATR, neat, cm^{-1}) 3324 (br, m), 2930 (m), 2871 (m), 2823 (m), 1426 (m), 1014 (s), 995 (s), 820 (m), 725 (s), 663 (s).



44

Synthesis of 44: Following the general procedure, the title compound was isolated as a yellow oil (47.2 mg, 95%).

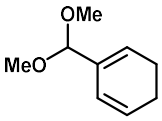
R_f = 0.42 (SiO_2, hexanes:EtOAc = 2:1, $KMnO_4$).

$_1$H NMR: (500 MHz, $CDCl_3$) δ 5.99 (dt, *J* = 9.9, 1.5 Hz, 1H), 5.88 (dtd, *J* = 9.9, 3.6, 1.5 Hz, 1H), 5.68 (dtd, *J* = 5.0, 3.6, 1.5 Hz, 1H), 4.25 (q, *J* = 6.4 Hz, 1H), 2.18 – 2.07 (m, 4H), 1.78 (br, 1H), 1.26 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 139.7, 127.7, 123.5, 120.1, 70.3, 22.5, 22.2, 22.1.

HRMS: (ESI-TOF, m/z) calcd. For $C_8H_{12}O$ $[M]^+$ calc.: 124.0888; found: 124.0888.

IR: (ATR, neat, cm^{-1}) 3339 (br), 2971 (m), 2872 (m), 2872 (m), 2823 (m), 1426 (m), 1066 (s), 945 (m), 819 (m), 598 (s).



45

Synthesis of 45: The reaction was conducted following the general procedure, except the neutralization after the hydrolysis of urazole moiety was not conducted. The title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 20:1) as a colorless oil (44.1 mg, 71%).

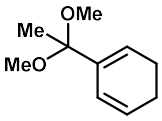
R_f = 0.27 (SiO_2, hexanes:EtOAc = 10:1, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.98 (d, *J* = 9.8 Hz, 1H), 5.93 – 5.89 (m, 1H), 5.88 – 5.86 (m, 1H), 4.65 (s, 1H), 3.30 (s, 6H), 2.25 – 2.18 (m, 2H), 2.19 – 2.10 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 133.2, 127.6, 124.7, 122.9, 104.4, 53.3, 22.3, 22.0.

HRMS: (ESI-TOF, m/z) calcd. For $C_9H_{15}O_2$ $[M+H]^+$ calc.: 155.1067; found: 155.1064.

IR: (ATR, neat, cm^{-1}) 2933 (w), 2825 (w), 1367 (w), 1193 (w), 1098 (m), 1075 (m), 1051 (s), 1000 (w), 945 (w), 813 (w).



46

Synthesis of 46: The reaction was conducted following the general procedure, except the neutralization after the hydrolysis of urazole moiety was not conducted. The title compound was isolated as a colorless oil (63.2 mg, 94%).

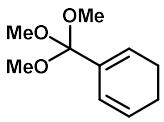
R_f = 0.47 (SiO_2, hexanes:EtOAc = 10:1, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.99 – 5.92 (m, 2H), 5.86 (ddt, *J* = 9.5, 5.0, 2.5 Hz, 1H), 3.14 (s, 6H), 2.25 – 2.13 (m, 2H), 2.13 – 2.02 (m, 2H), 1.33 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 136.8, 127.1, 123.7, 123.1, 100.8, 48.8, 23.1, 22.2, 22.1.

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{16}O_2$ $[M+Na]^+$ calc.: 191.1043; found: 191.1036.

IR: (ATR, neat, cm^{-1}) 2937 (w), 2827 (w), 1272 (m), 1190 (m), 1142 (s), 1066 (s), 1051 (s), 1031 (s), 872 (s), 629 (m).



47

Synthesis of 47: The reaction was conducted following the general procedure, except the neutralization after the hydrolysis of urazole moiety was not conducted. The title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 20:1) as a colorless oil (65.3 mg, 89%).

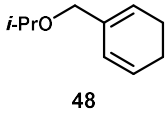
R_f = 0.31 (SiO_2, hexanes:EtOAc = 10:1, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.13 (tt, *J* = 4.3, 1.5 Hz, 1H), 5.96 (dt, *J* = 9.8, 1.5 Hz, 1H), 5.87 (dtd, *J* = 9.8, 4.3, 1.0 Hz, 1H), 3.13 (s, 9H), 2.25 – 2.20 (m, 2H), 2.17 – 2.07 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 131.3, 127.3, 127.3, 123.1, 114.2, 49.5, 22.1, 22.0.

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{20}NO_3$ $[M+NH_4]^+$ calc.: 202.1438; found: 202.1433.

IR: (ATR, neat, cm^{-1}) 2942 (w), 2823 (w), 1437 (w), 1270 (m), 1183 (w), 1088 (s), 1061 (s), 1038 (m), 833 (w), 748 (w).



48

Synthesis of 48: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 20:1) as a colorless oil (35.6 mg, 58%).

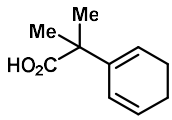
R_f = 0.49 (SiO_2, hexanes:EtOAc = 10:1, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.94 (ddd, *J* = 8.2, 1.5 Hz, 1H), 5.89 – 5.83 (m, 1H), 5.71 (ddt, *J* = 4.2, 2.8, 1.5 Hz, 1H), 3.90 (d, *J* = 1.5 Hz, 2H), 3.59 (sept, *J* = 6.1 Hz, 1H), 2.25 – 2.05 (m, 4H), 1.15 (d, *J* = 6.1 Hz, 6H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 133.6, 127.2, 125.2, 123.0, 72.2, 70.6, 22.4, 22.3, 22.2.

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{16}O$ $[M]^+$ calc.: 152.1196; found: 152.1197.

IR: (ATR, neat, cm^{-1}) 3039 (w), 2917 (s), 2875 (m), 2859 (m), 1356 (w), 1240 (w), 1095 (m), 1066 (m), 821 (w), 734 (w).



49

Synthesis of 49: Following the general procedure using **20** (99.7 mg, 0.34 mmol, 1.0 eq.), the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 6:1) as a colorless oil (55.1 mg, 97%).

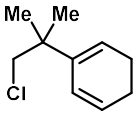
R_f = 0.47 (SiO_2, hexanes:EtOAc = 2:1, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 11.33 (br, 1H), 5.93 (d, *J* = 9.8 Hz, 1H), 5.87 (dt, *J* = 9.8, 4.2 Hz, 1H), 5.70 (t, *J* = 4.2 Hz, 1H), 2.26 – 2.19 (m, 2H), 2.17 – 2.09 (m, 2H), 1.34 (s, 6 H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 185.3 (detected from HMBC), 138.2, 127.5, 124.6, 119.8, 47.6 (detected from HMBC), 24.5, 22.6, 22.0.

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{14}O_2$ $[M]^+$ calc.: 166.0994; found: 166.0991.

IR: (ATR, neat, cm^{-1}) 3039 (w), 2917 (s), 2875 (m), 2859 (m), 1356 (w), 1240 (w), 1095 (m), 1066 (m), 821 (w), 734 (w).



50

Synthesis of 50: Following the general procedure, the title compound was isolated as a colorless oil (54.4 mg, 90%).

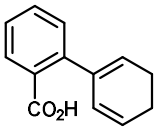
R_f = 0.70 (SiO_2, hexanes:EtOAc = 10:1, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.98 (dd, *J* = 9.7, 2.1 Hz, 1H), 5.90 (dt, *J* = 9.7, 4.2 Hz, 1H), 5.65 (t, *J* = 4.5 Hz, 1H), 3.44 (s, 2H), 2.19 – 2.11 (m, 2H), 2.10 – 2.02 (m, 2H), 1.14 (s, 6H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 139.5, 127.6, 123.9, 120.4, 54.6, 39.2, 24.6, 22.7, 22.1.

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{15}Cl$ $[M]^+$ calc.: 170.0862; found: 170.0861.

IR: (ATR, neat, cm^{-1}) 3042 (w), 2974 (w), 2933 (w), 2875 (w), 2829 (w), 1466 (w), 1366 (w), 1281 (w), 1061 (w), 814 (w), 746 (w), 711 (m), 600 (m).



51

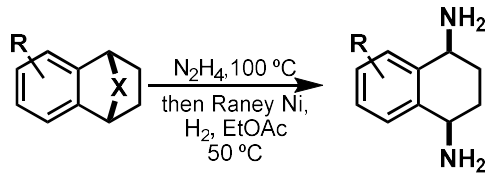
Synthesis of 51: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, hexanes:EtOAc = 1:1) as an off-white oil (48.8 mg, 61%).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 11.55 (br, 1H), 7.90 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.49 (td, *J* = 7.7, 1.4 Hz, 1H), 7.34 (td, *J* = 7.7, 1.4 Hz, 1H), 7.29 (dd, *J* = 7.7, 1.4 Hz, 1H), 5.95 (dd, *J* = 9.7, 1.7 Hz, 1H), 5.92 – 5.84 (m, 1H), 5.83 – 5.76 (m, 1H), 2.32 (m, 2H), 2.22 (m, 2H).

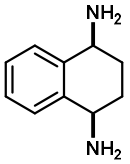
^{13}C NMR: (126 MHz, $CDCl_3$) δ 172.7, 143.7, 137.4, 132.8, 130.6, 130.0, 130.1, 127.3, 127.0, 126.1, 124.0, 23.6, 22.9.

The analytical data was in accordance with previously reported values.[37]

N,N-bond fragmentation of polynuclear cycloadducts



A mixture of cycloadduct (0.2 mmol, 1.0 equiv.) and anhydrous hydrazine (0.125 mL, 4.0 mmol, 20 equiv.) was stirred at 100 °C until full conversion of the cycloadduct was observed. The reaction was then cooled to 50 °C, and ethanol (1 mL) was added under an atmosphere of H_2 (balloon). Raney®-Nickel (0.1 mL, W.R. Grace and Co. Raney® 2400, slurry, in H_2O) was added, and the resulting mixture was stirred under a hydrogen atmosphere at 50 °C for 8 h, then filtered through a plug of Celite. The product was purified by column chromatography (SiO_2, 5% NH_4OH (5.0 M, aq) in MeOH) to provide compound diamine.



52

Synthesis of 52: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, 5% NH_4OH (5 M, aq) in MeOH) as a brown oil (25.0 mg, 77%).

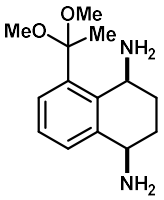
R_f = 0.26 (SiO, 5% NH_4OH (5 M, aq) in MeOH, ninhydrin).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 5.7, 3.4 Hz, 2H), 7.24 (dd, *J* = 5.7, 3.4 Hz, 2H), 3.94 (t, *J* = 5.5 Hz, 2H), 2.03 – 1.97 (m, 2H), 1.91 (br, 4H), 1.85 – 1.78 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 140.9, 127.9, 127.4, 49.8, 30.2.

HRMS: (ESI-TOF, m/z) calcd. For $C_{10}H_{14}KN_2$ $[M+K]^+$ calc.: 201.0789; found: 201.0785.

IR: (ATR, neat, cm^{-1}) 3277 (br, m), 2928 (m), 1571 (s), 1449 (s), 1370 (m), 1350 (m), 940 (w), 771 (m), 722 (w).



53

Synthesis of 53: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, 5% NH_4OH (5 M, aq) in MeOH) as a brown oil (29.4 mg, 59%).

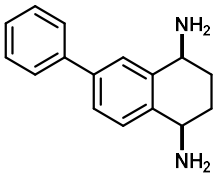
R_f = 0.10 (SiO_2, 5% NH_4OH (5 M, aq) in MeOH, ninhydrin).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 2H), 7.21 (t, *J* = 7.7 Hz, 1H), 4.46 (d, *J* = 3.2 Hz, 1H), 4.00 (t, *J* = 7.5 Hz, 1H), 3.35 (s, 3H), 3.15 (s, 3H), 2.10 – 2.08 (m, 5H), 2.06 – 1.97 (m, 1H), 1.95 – 1.85 (m, 1H), 1.80 – 1.70 (m, 1H), 1.54 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 142.3, 141.1, 140.2, 128.8, 127.1, 126.5, 104.1, 51.0, 49.7, 48.7, 46.1, 30.1, 27.8, 26.0.

HRMS: (ESI-TOF, m/z) calcd. For $C_{14}H_{22}N_2NaO_2$ $[M+Na]^+$ calc.: 273.1573; found: 273.1562.

IR: (ATR, neat, cm^{-1}) 3360 (br, w), 2933 (m), 1580 (m), 1460 (m), 1371 (m), 1265 (m), 1143 (s), 1088 (s), 870 (m), 759 (m).



54

Synthesis of 54: Following the general procedure E, the title compound was isolated by flash chromatography (SiO_2, 5% NH_4OH (5 M, aq) in MeOH) as a brown oil (30.4 mg, 65%).

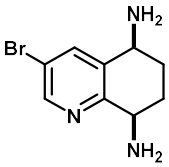
R_f = 0.26 (SiO_2, 5% NH_4OH (5 M, aq) in MeOH, ninhydrin).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 1.8 Hz, 1H), 7.62 – 7.57 (m, 2H), 7.53 – 7.46 (m, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 4.08 – 3.88 (m, 2H), 2.10 – 2.00 (m, 2H), 1.92 – 1.82 (m, 2H), 1.70 (br, 4H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 141.2, 141.1, 140.3, 139.9, 128.9, 128.4, 127.4, 127.2, 126.6, 126.1, 49.8, 49.5, 30.3, 30.2.

HRMS: (ESI-TOF, m/z) calcd. For $C_{16}H_{19}N_2$ $[M+H]^+$ calc.: 239.1543; found: 239.1533.

IR: (ATR, neat, cm^{-1}) 3353 (w), 2924 (m), 2885 (m), 1599 (m), 1482 (s), 904 (m), 830 (s), 766 (s), 756 (s), 698 (s).



55

Synthesis of 55: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, 5% NH_4OH (5 M, aq) in MeOH) as a brown oil (26.0 mg, 54%).

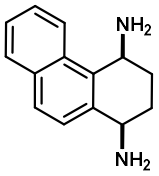
R_f = 0.03 (SiO_2, 5% NH_4OH (5 M, aq) in MeOH, ninhydrin).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 2.2 Hz, 1H), 7.94 (d, *J* = 2.2 Hz, 1H), 4.03 – 3.73 (m, 2H), 2.10 (dddd, *J* = 14.2, 9.0, 5.8, 3.3 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.92 – 1.86 (m, 1H), 1.86 – 1.78 (m, 1H), 1.69 (br, 4H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 157.8, 149.2, 138.7, 137.5, 119.1, 51.0, 49.5, 30.2, 27.7.

HRMS: (ESI-TOF, m/z) calcd. For $C_9H_{12}BrN_3$ [M]+ calc.: 241.0209; found: 241.0212.

IR: (ATR, neat, cm^{-1}) 3349 (w), 2934 (m), 2856 (m), 1685 (m), 1588 (m), 1437 (s), 899 (s), 858 (m), 781 (m), 625 (w).



56

Synthesis of 56: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, 5% NH_4OH (5 M, aq) in MeOH) as a brown oil (41.4 mg, 97%).

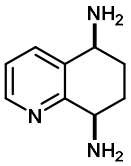
R_f = 0.26 (SiO_2, 5% NH_4OH (5 M, aq) in MeOH, ninhydrin).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.6 Hz, 1H), 7.81 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.54 (ddd, *J* = 8.6, 6.8, 1.4 Hz, 1H), 7.46 (dd, *J* = 8.1, 6.8 Hz, 1H), 4.74 (t, *J* = 3.2 Hz, 1H), 4.04 (dd, *J* = 10.2, 5.9 Hz, 1H), 2.17 – 2.09 (m, 1H), 2.09 – 2.02 (m, 2H), 2.00 – 1.90 (m, 1H), 1.85 (br s, 4H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 138.1, 134.9, 133.0, 131.7, 128.8, 127.9, 126.7, 125.4, 125.3, 123.7, 50.9, 45.0, 31.0, 29.0.

HRMS: (ESI-TOF, m/z) calcd. For $C_{14}H_{20}N_3$ $[M+NH_4]^+$ calc.: 230.1652; found: 230.1661.

IR: (ATR, neat, cm^{-1}) 3276 (br, w), 2924 (m), 2856 (m), 1597 (m), 1507 (m), 1198 (w), 906 (m), 817 (s), 751 (s), 732 (s).



57

Synthesis of 57: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, 5% NH_4OH (5 M, aq) in MeOH) as a brown oil (34.0 mg, 92%).

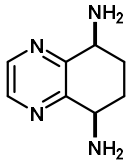
R_f = 0.09 (SiO_2, 5% NH_4OH (5 M, aq) in MeOH, ninhydrin).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.74 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.16 (dd, *J* = 7.8, 4.7 Hz, 1H), 4.02 – 3.94 (m, 2H), 2.11 (dddd, *J* = 13.2, 8.4, 5.3, 3.3 Hz, 1H), 2.03 (dddd, *J* = 13.2, 9.9, 5.3, 3.3 Hz, 1H), 1.95 – 1.85 (m, 1H), 1.84 (tdd, *J* = 8.4, 5.3, 2.6 Hz, 1H), 1.77 (br s, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 148.3, 136.4, 135.5, 122.4, 51.5, 49.5, 30.3, 27.7.

IR (ATR, neat, cm^{-1}): 3349 (m), 3275 (m), 2927 (m), 2857 (w), 1574 (s), 1437 (s), 1372 (m), 942 (m), 808 (m), 728 (m).

HRMS (EI-TOF, m/z) calcd. For $C_9H_{17}N_4$ $[M+NH_4]^+$ calc.: 181.1448; found: 181.1445.



58

Synthesis of 58: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, 5% NH_4OH (5 M, aq) in MeOH) as a brown oil (17.4 mg, 53%).

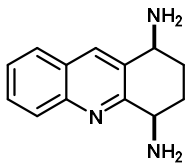
R_f = 0.12 (SiO_2, 5% NH_4OH (5 M, aq) in MeOH, ninhydrin).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.44 (s, 2H), 4.13 – 4.01 (m, 2H), 2.19 – 2.09 (m, 2H), 1.99 – 1.91 (m, 2H), 1.84 (br, 4H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 154.7, 143.1, 51.3, 27.7

HRMS: (ESI-TOF, m/z) calcd. For $C_8H_{12}N_4Na$ $[M+Na]^+$ calc.: 187.0954; found: 187.0954.

IR: (ATR, neat, cm^{-1}) 3352(s), 3284 (s), 2944 (w), 1594 (m), 1407 (m), 1375 (w), 1151 (w), 1069 (w), 947 (m), 629 (w).



59

Synthesis of 59: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, 5% NH_4OH (5 M, aq) in MeOH) as a brown oil (31.8 mg, 75%).

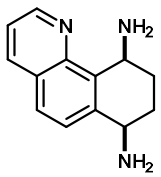
R_f = 0.41 (SiO_2, 5% NH_4OH (5 M, aq) in MeOH, ninhydrin).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.78 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.66 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.48 (dd, *J* = 8.1, 6.8 Hz, 1H), 4.21 – 4.16 (m, 1H), 4.13 (dd, *J* = 8.0, 5.7 Hz, 1H), 2.23 (dddd, *J* = 13.3, 7.5, 5.7, 4.0 Hz, 1H), 2.13 (ddd, *J* = 13.3, 9.1, 4.0 Hz, 1H), 1.98 (br, 4H), 1.97 – 1.85 (m, 2H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 160.7, 147.2, 134.9, 134.2, 129.3, 128.7, 127.7, 127.5, 126.3, 52.0, 49.7, 30.4, 27.9.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{15}N_3Na$ $[M+Na]^+$ calc.: 236.1158; found: 236.1164.

IR: (ATR, neat, cm^{-1}) 3350 (m), 2937 (w), 1597 (m), 1491 (m), 1446 (w), 1374 (w), 918 (m), 793 (m), 760 (s), 480 (w).



60

Synthesis of 60: Following the general procedure, the title compound was isolated by flash chromatography (SiO_2, 5% NH_4OH (5 M, aq) in MeOH) as a brown oil (24.8 mg, 58%).

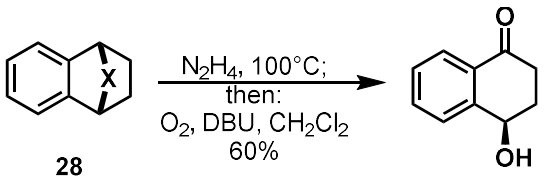
R_f = 0.20 (SiO_2, 5% NH_4OH (5 M, aq) in MeOH, ninhydrin).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.91 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.11 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 1H), 7.38 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.98 (t, *J* = 4.3 Hz, 1H), 4.06 (dd, *J* = 9.2, 4.7 Hz, 1H), 2.15 – 2.06 (m, 3H), 2.01 – 1.95 (m, 1H), 1.94 (br, 4H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 149.6, 147.1, 141.7, 137.5, 136.4, 127.4, 126.8, 126.6, 120.8, 51.0, 45.2, 30.1, 29.4.

HRMS: (ESI-TOF, m/z) calcd. For $C_{13}H_{15}N_3$ $[M]^+$ calc.: 213.1260; found: 213.1251.

IR: (ATR, neat, cm^{-1}) 3347 (w), 2927 (m), 2857 (w), 1595 (m), 1498 (m), 1455 (m), 1370 (w), 942 (w), 838 (s), 812 (s).



28 **63**

Compound **28** (50.0 mg, 0.21 mmol, 1.0 eq) and anhydrous hydrazine (0.125 mL, 4.11 mmol, 20.0 eq) under a nitrogen atmosphere was heated at 100 ºC for 8 h. Reaction was then cooled to rt, and hydrazine was removed at 50 ºC *in vacuo*. Dichloromethane (10 mL) was added to dissolve the residue, and oxygen gas was bubble through the reaction at rt for 15 minutes. After stirring the mixture under oxygen atmosphere for 4 h, 1,8-diazabicyclo[5.4.0]undec-7-ene (92 µL, 0.62 mmol, 3.0 eq) was added, and the reaction was further stirred for 45 minutes. The reaction was quenched with aqueous saturated ammonium chloride solution (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), dried over magnesium sulfate, and concentrated in vacuo. The crude mixture was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 1:1) to afford the titled compound **63** as a brown oil (20.1 mg, 60%).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 1H), 7.64 – 7.55 (m, 2H), 7.41 (ddd, J = 8.1, 5.1, 3.4 Hz, 1H), 4.98 (dd, J = 7.8, 3.9 Hz, 1H), 2.93 (ddd, J = 17.4, 7.8, 4.5 Hz, 1H), 2.59 (ddd, J = 17.4, 9.6, 4.5 Hz, 1H), 2.40 (ddt, J = 13.0, 7.8, 4.5 Hz, 1H), 2.35 (br, 1H), 2.18 (dddd, J = 13.0, 9.6, 7.8, 4.5 Hz, 1H).

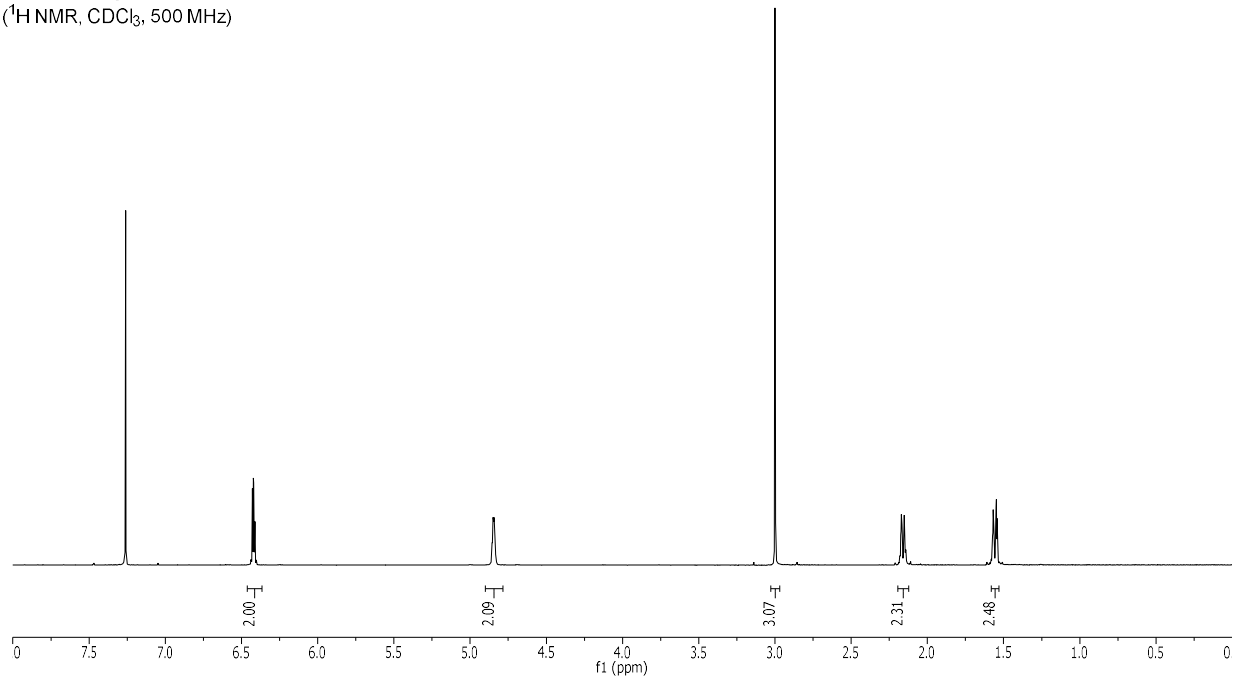
^{13}C NMR: (126 MHz, $CDCl_3$) δ 197.7, 145.5, 134.2, 131.2, 128.5, 127.3, 127.2, 68.0, 35.3, 32.2.

The analytical data was in accordance with previously reported values.[38]

^{1}H and ^{13}C NMR Spectra

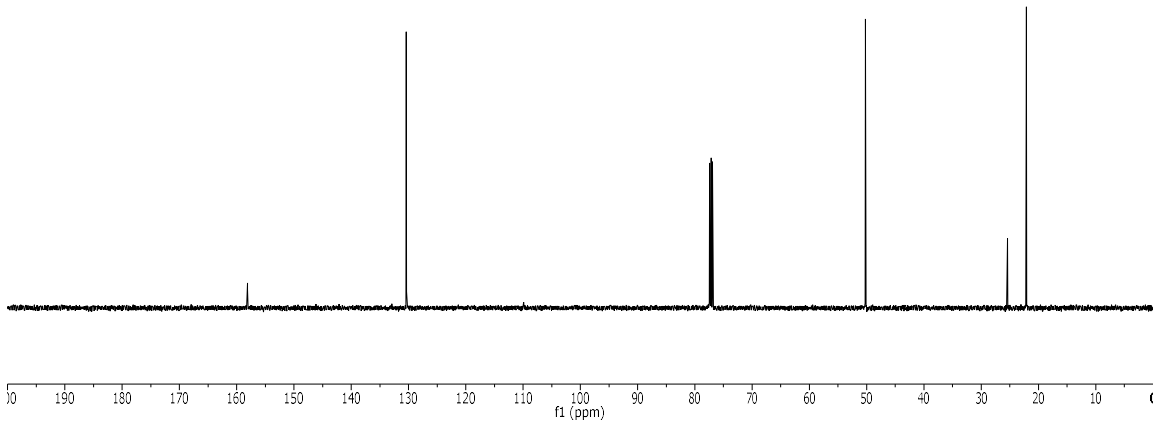
6

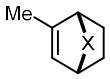
(^{1}H NMR, $CDCl_3$, 500 MHz)



6

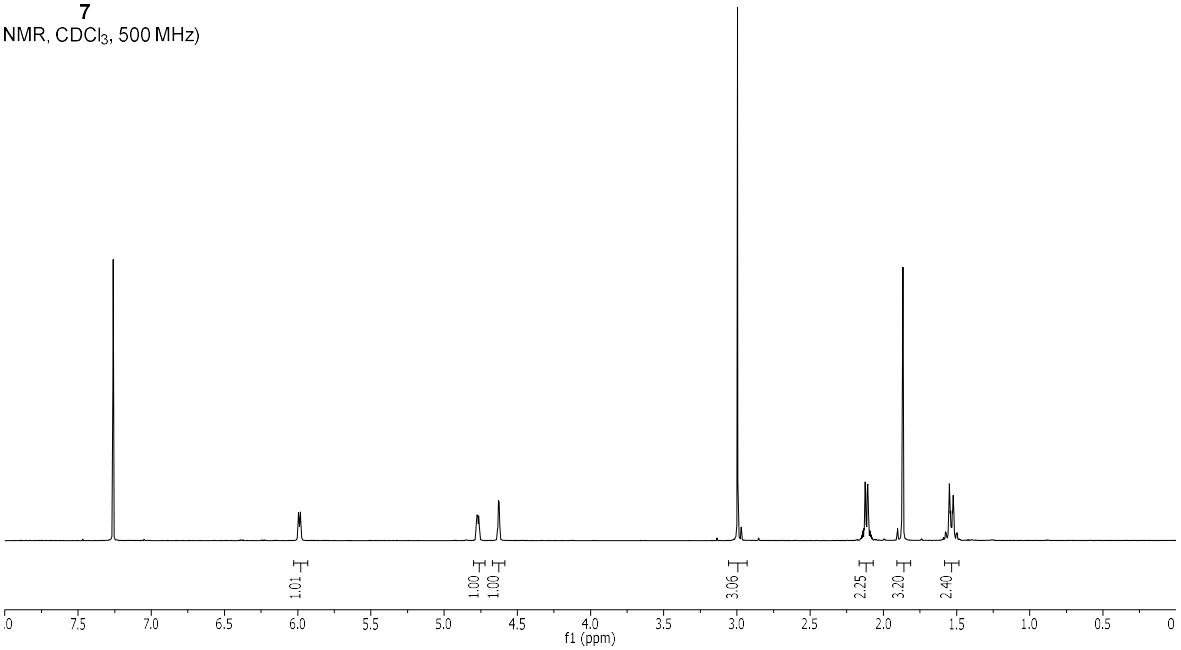
(^{13}C NMR, $CDCl_3$, 126 MHz)





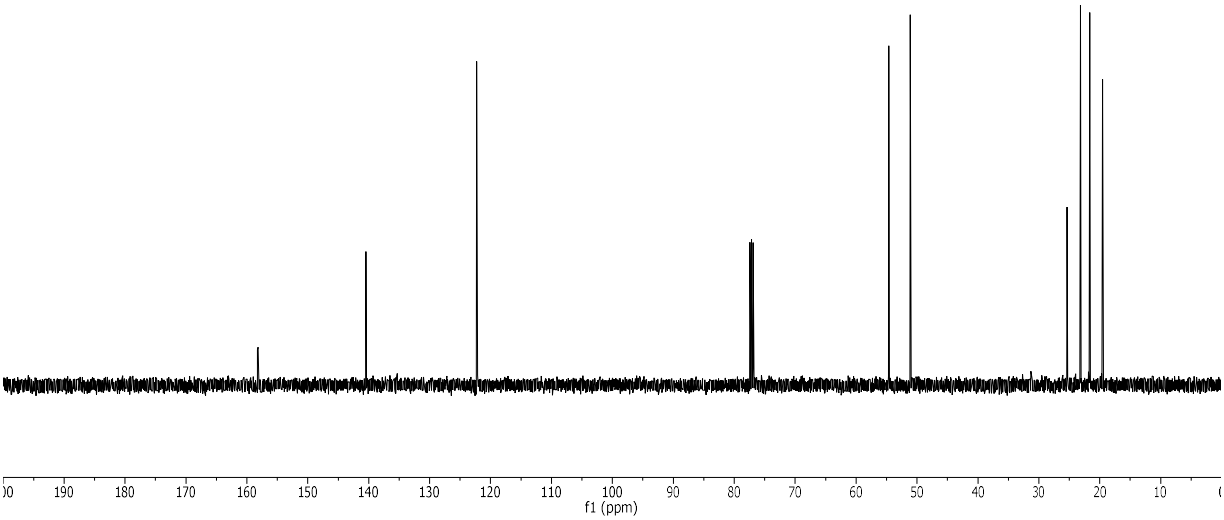
7

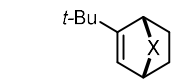
(^{1}H NMR, $CDCl_3$, 500 MHz)



7

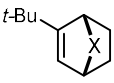
(^{13}C NMR, $CDCl_3$, 126 MHz)





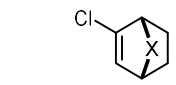
8

(^{1}H NMR, $CDCl_3$, 500 MHz)



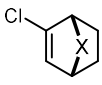
8

(^{13}C NMR, $CDCl_3$, 126 MHz)



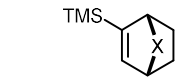
9

(^{1}H NMR, $CDCl_3$, 500 MHz)



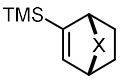
9

(^{13}C NMR, $CDCl_3$, 126 MHz)



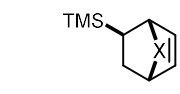
10

(^{1}H NMR, $CDCl_3$, 500 MHz)



10

(^{13}C NMR, $CDCl_3$, 126 MHz)

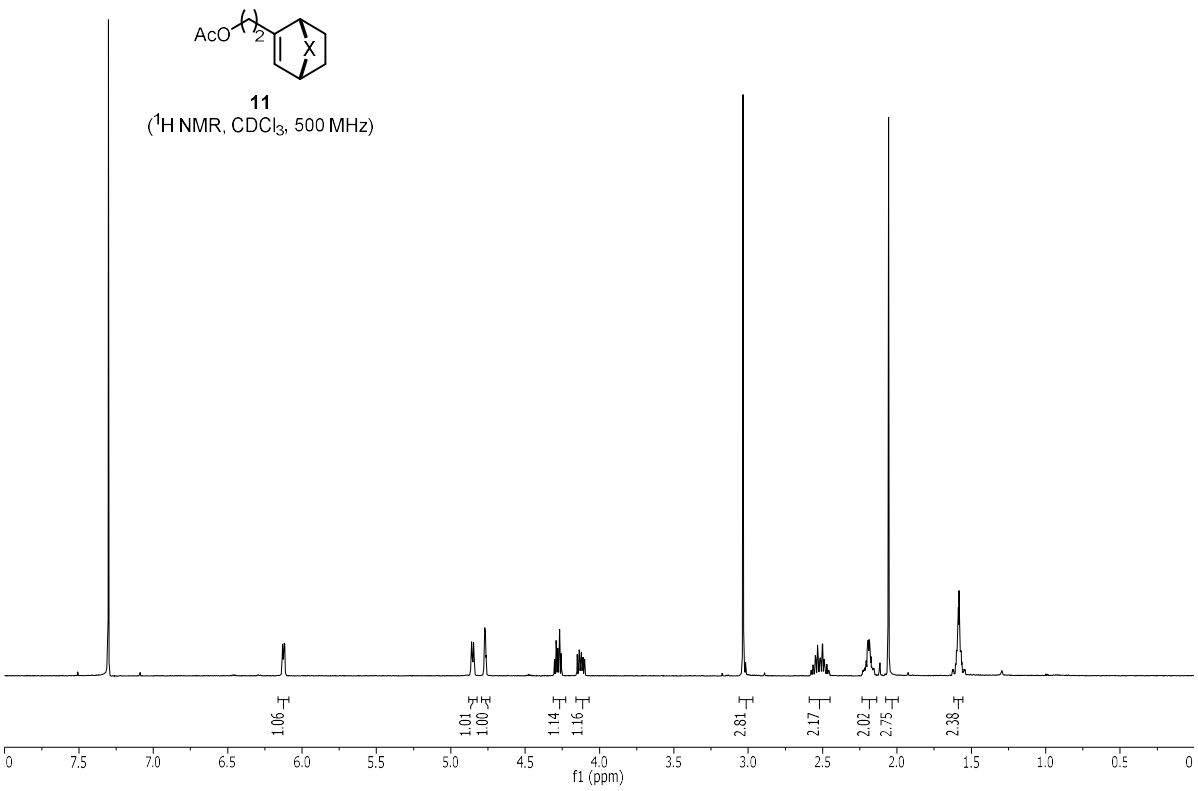


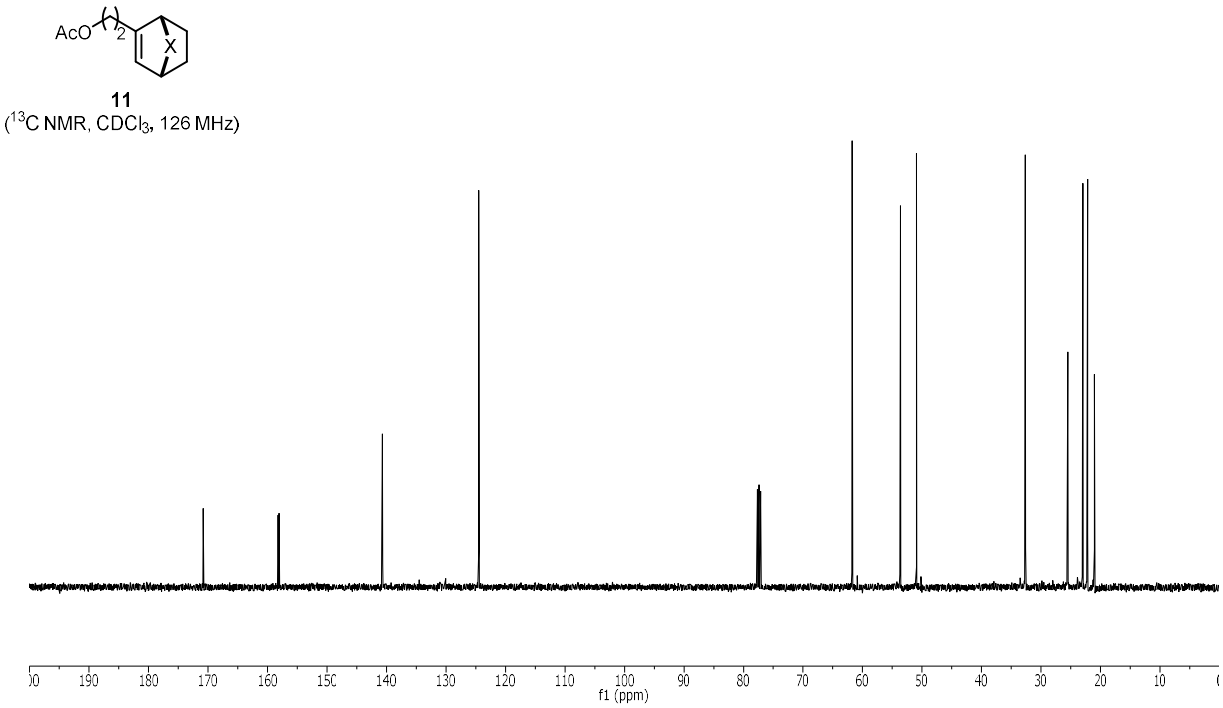
10'

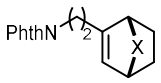
(^{1}H NMR, $CDCl_3$, 500 MHz)

10'

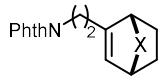
(^{13}C NMR, $CDCl_3$, 126 MHz)


AcO
2
X
11
(1H NMR, CDCl3, 500 MHz)
1.06
1.01
1.00
1.14
1.16
2.81
2.17
2.02
2.75
2.38
f1 (ppm)

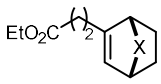

AcO
2
X
11
(13C NMR, CDCl3, 126 MHz)
f1 (ppm)



12
(^{1}H NMR, $CDCl_3$, 500 MHz)

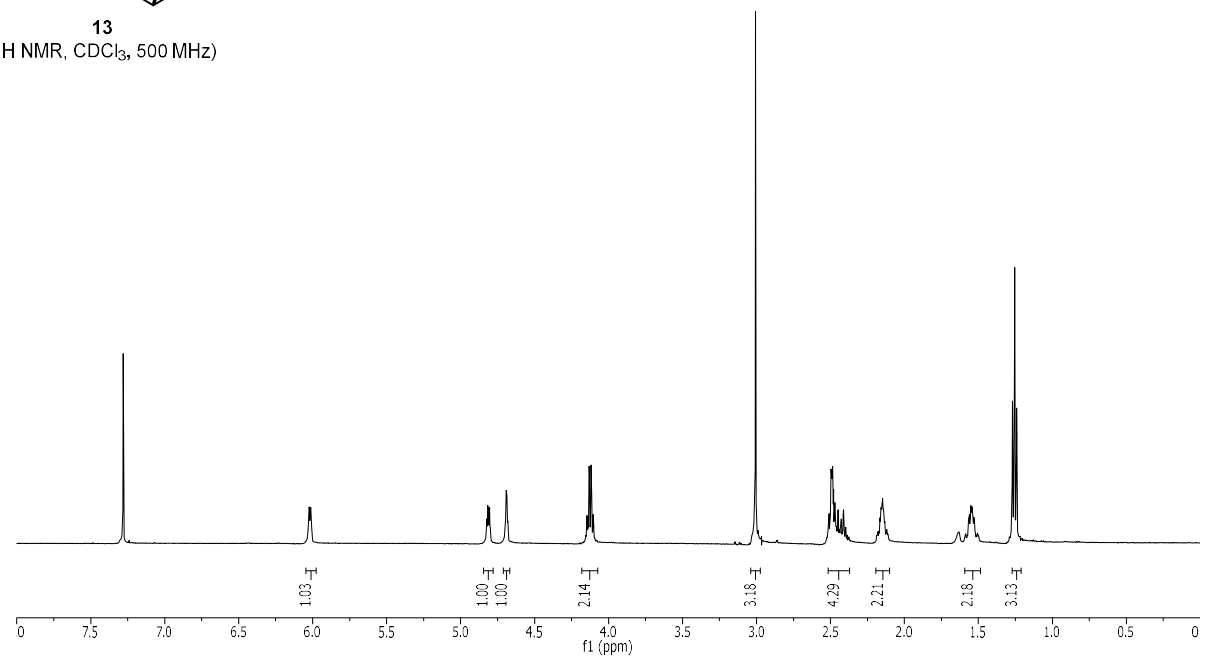


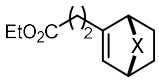
12
(^{13}C NMR, $CDCl_3$, 126 MHz)



13

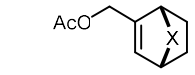
(^{1}H NMR, $CDCl_3$, 500 MHz)





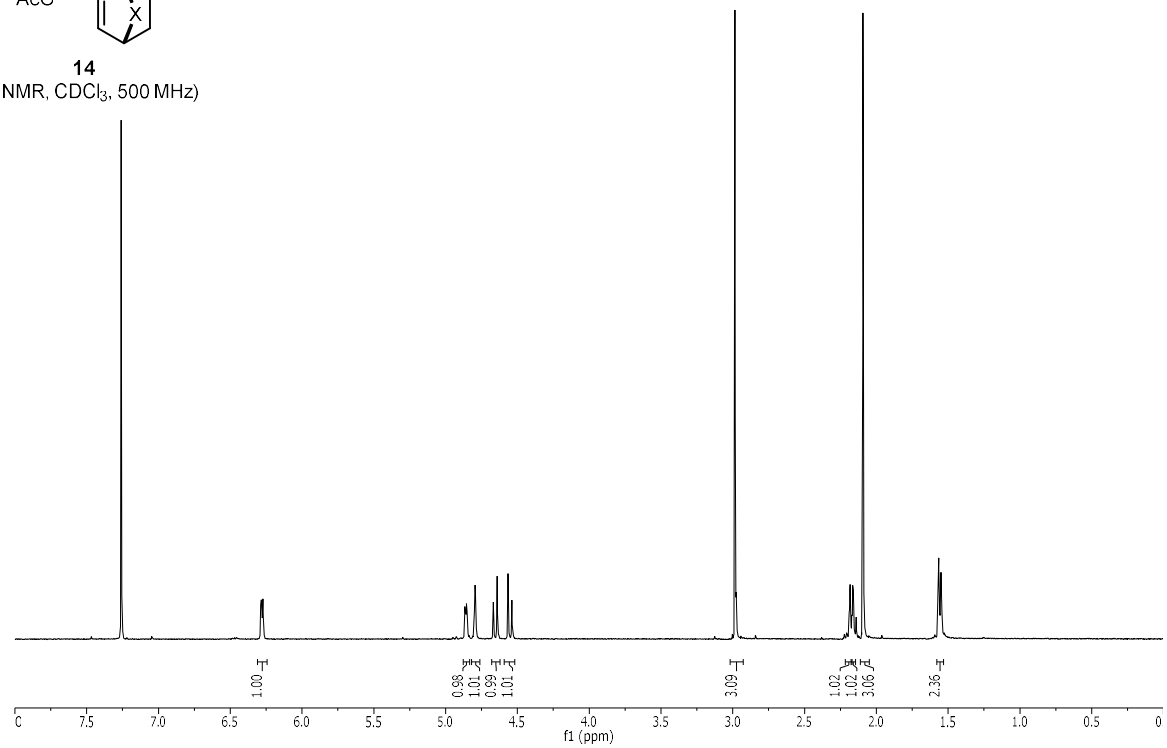
13

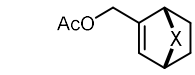
(^{13}C NMR, $CDCl_3$, 126 MHz)



14

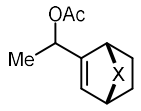
(^{1}H NMR, $CDCl_3$, 500 MHz)



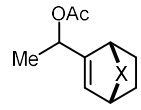


14

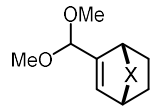
(^{13}C NMR, $CDCl_3$, 126 MHz)



15
dr = 1.5 : 1
(^{1}H NMR, $CDCl_3$, 500 MHz)

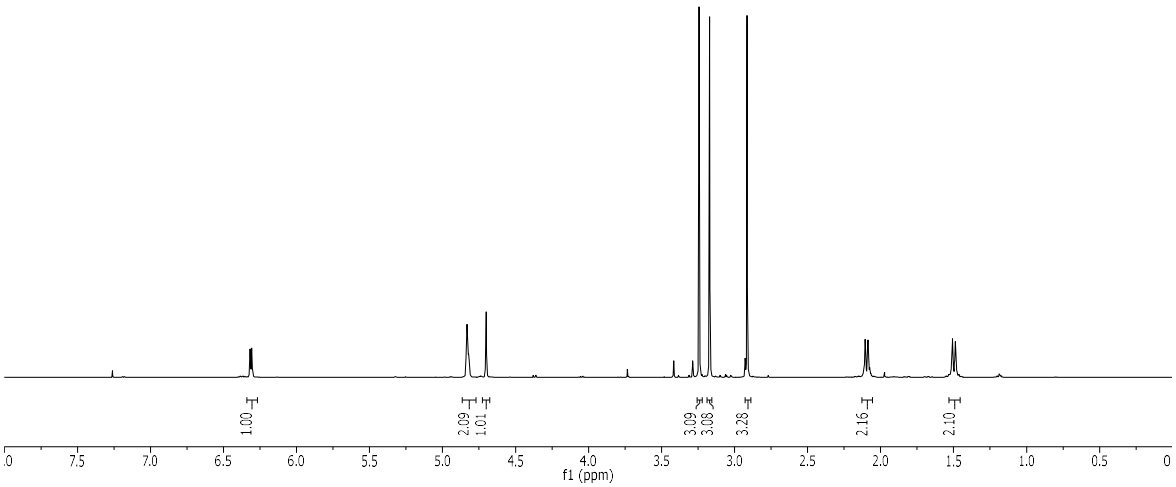


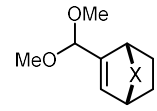
15
dr = 1.5 : 1
(^{13}C NMR, $CDCl_3$, 126 MHz)



16

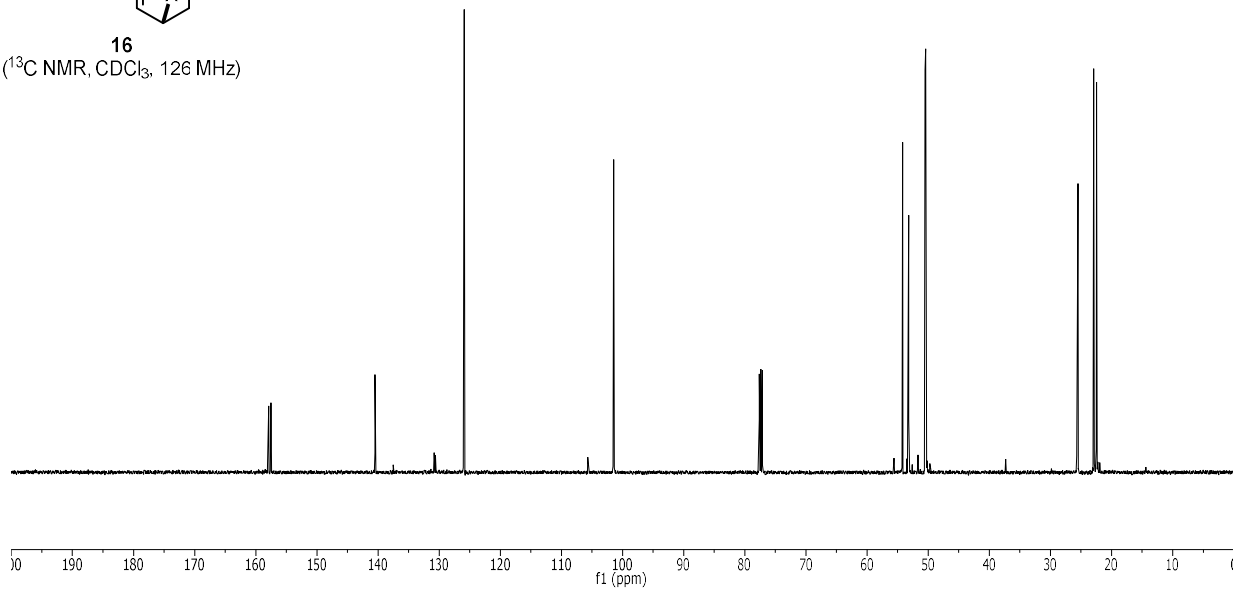
(^{1}H NMR, $CDCl_3$, 500 MHz)

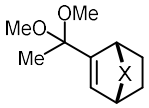




16

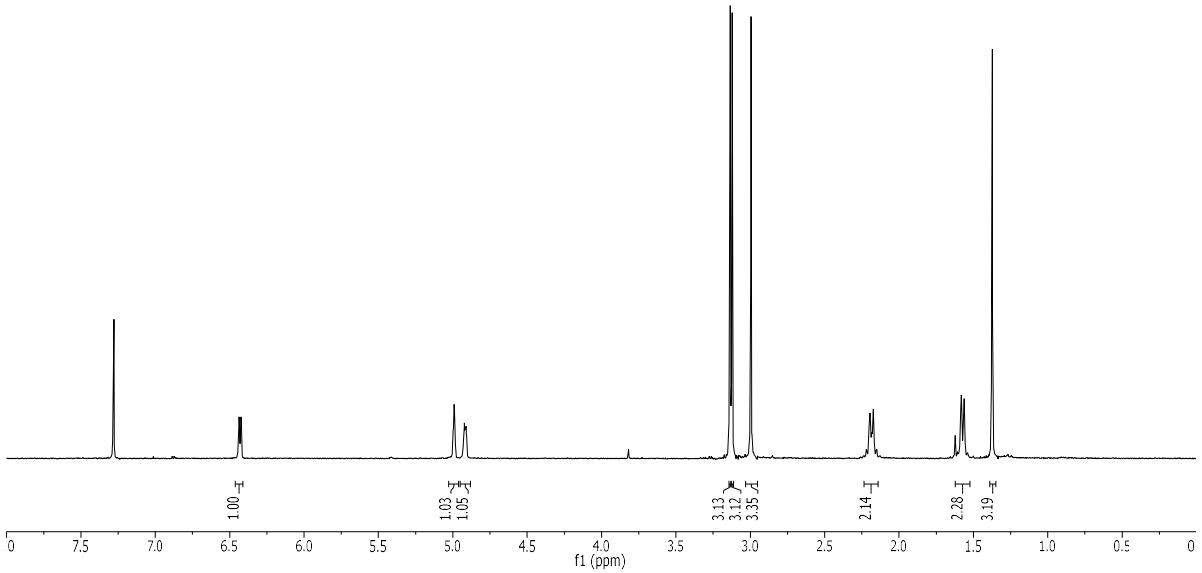
(^{13}C NMR, $CDCl_3$, 126 MHz)

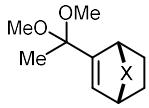




17

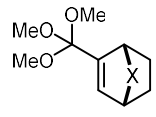
(^{1}H NMR, $CDCl_3$, 500 MHz)



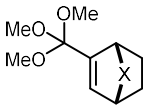


17

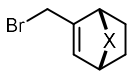
(^{13}C NMR, $CDCl_3$, 126 MHz)



18
(^{1}H NMR, $CDCl_3$, 500 MHz)

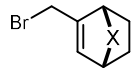


18
(^{13}C NMR, $CDCl_3$, 126 MHz)



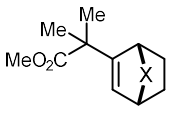
19

(^{1}H NMR, $CDCl_3$, 500 MHz)

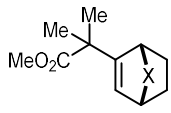


19

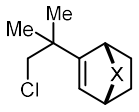
(^{13}C NMR, $CDCl_3$, 126 MHz)



20
(^{1}H NMR, $CDCl_3$, 500 MHz)

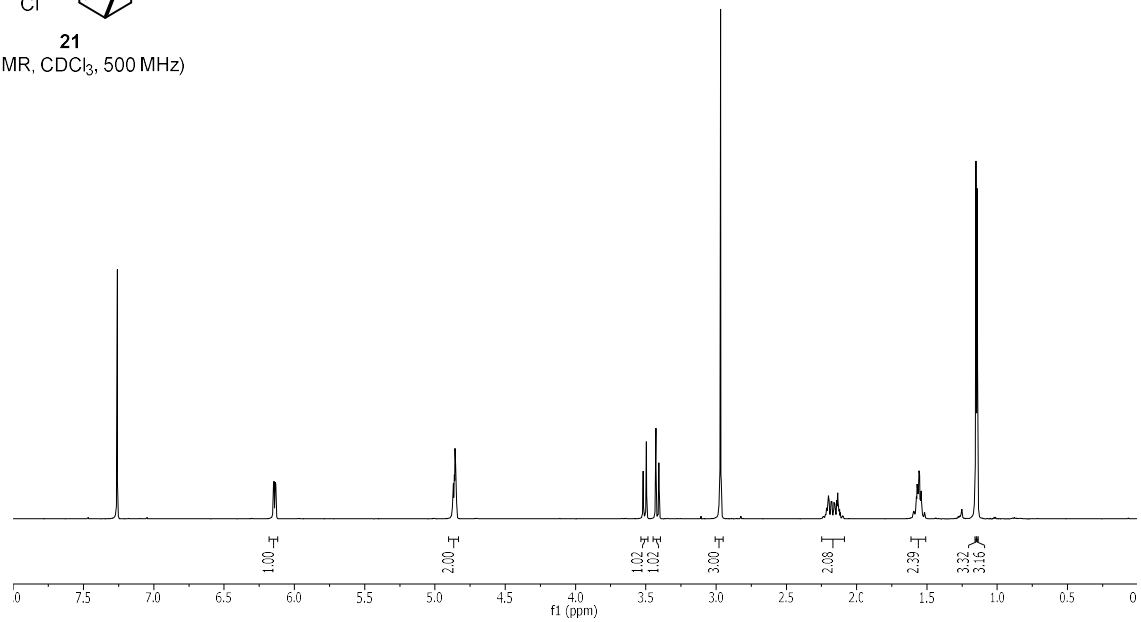


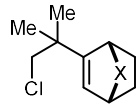
20
(^{13}C NMR, $CDCl_3$, 126 MHz)



21

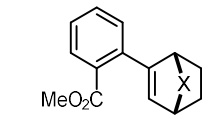
(^{1}H NMR, $CDCl_3$, 500 MHz)



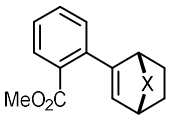


21

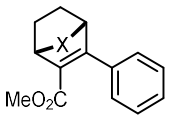
(^{13}C NMR, $CDCl_3$, 126 MHz)



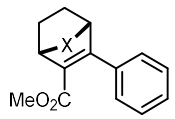
22
(^{1}H NMR, $CDCl_3$, 500 MHz)



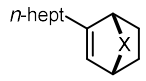
22
(^{13}C NMR, $CDCl_3$, 126 MHz)



22'
(^{1}H NMR, $CDCl_3$, 500 MHz)

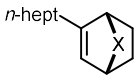


22'
(^{13}C NMR, $CDCl_3$, 126 MHz)



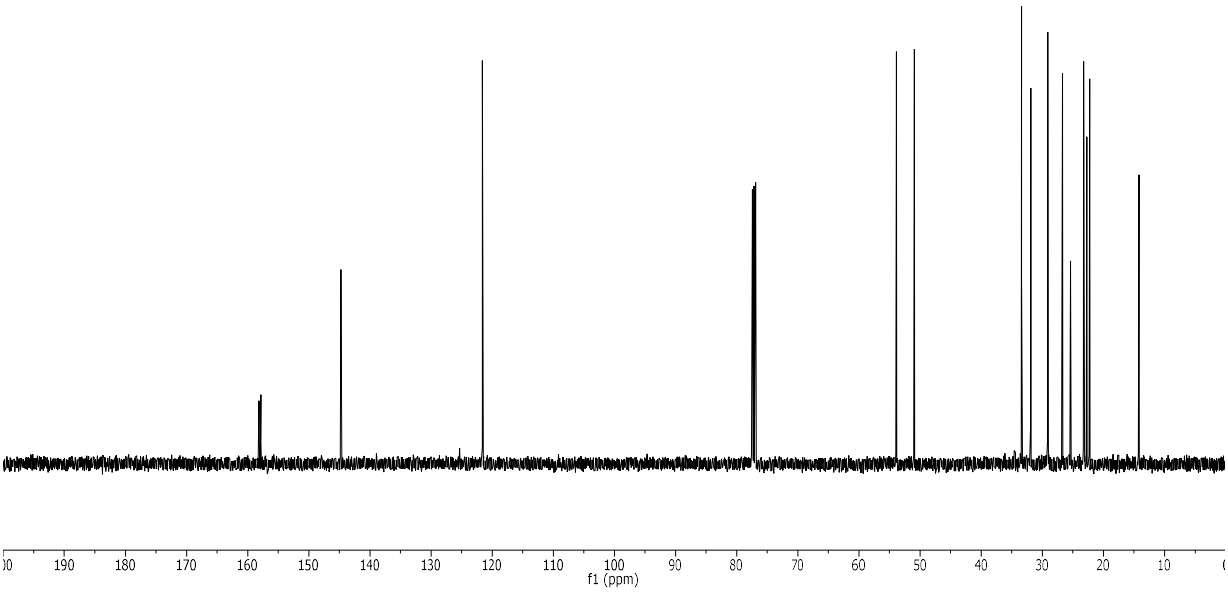
23

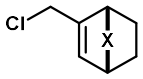
(^{1}H NMR, $CDCl_3$, 500 MHz)



23

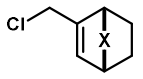
(^{13}C NMR, $CDCl_3$, 126 MHz)





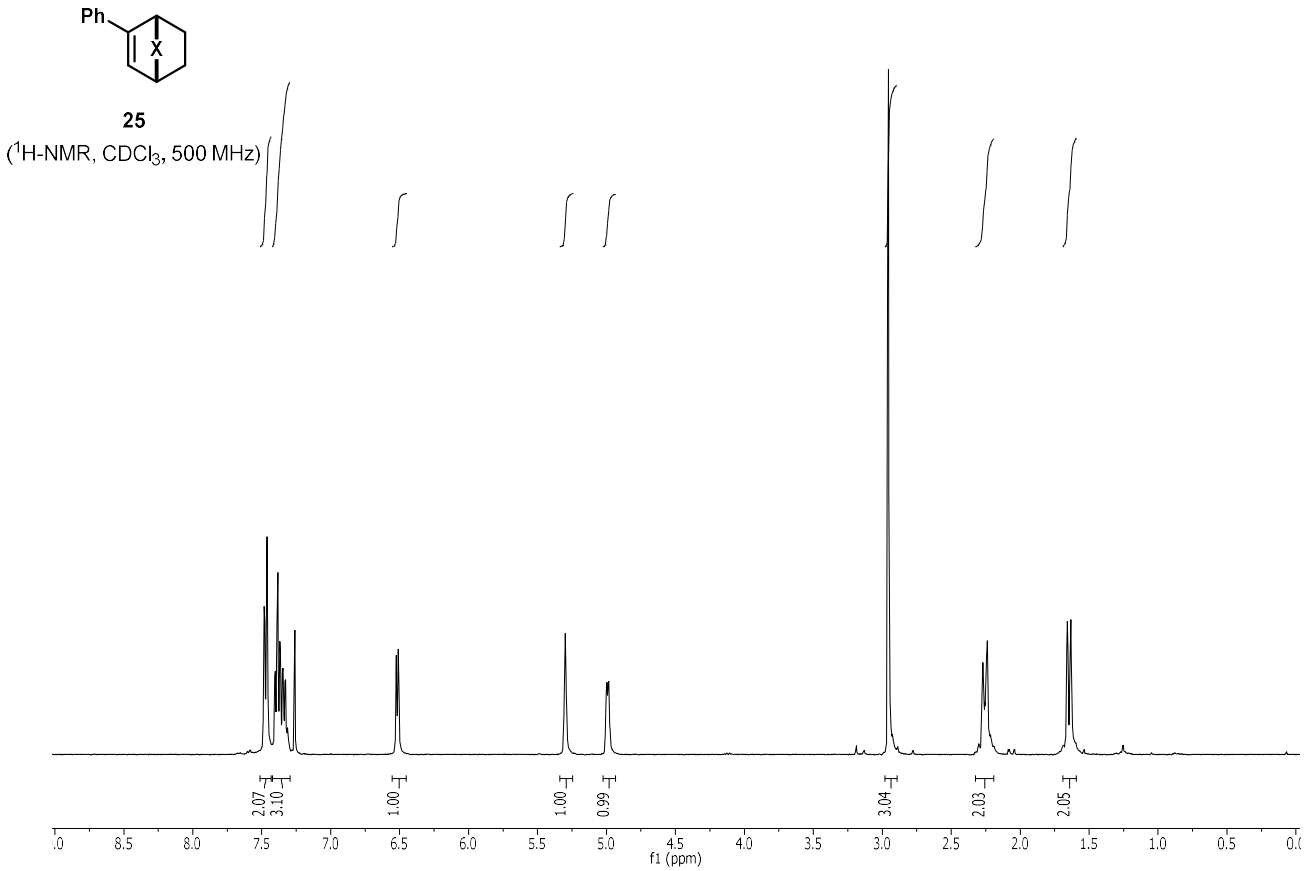
24

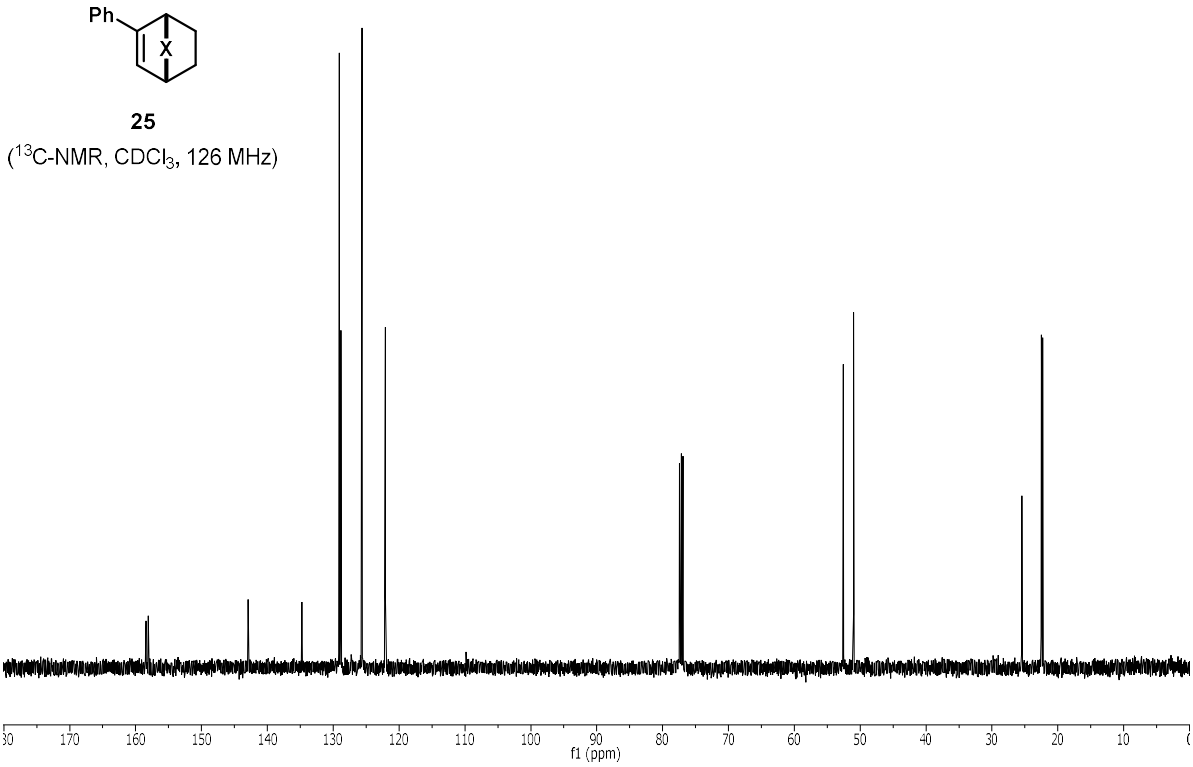
(^{1}H-NMR, $CDCl_3$, 500 MHz)

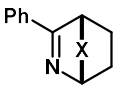


24

(^{13}C-NMR, $CDCl_3$, 126 MHz)

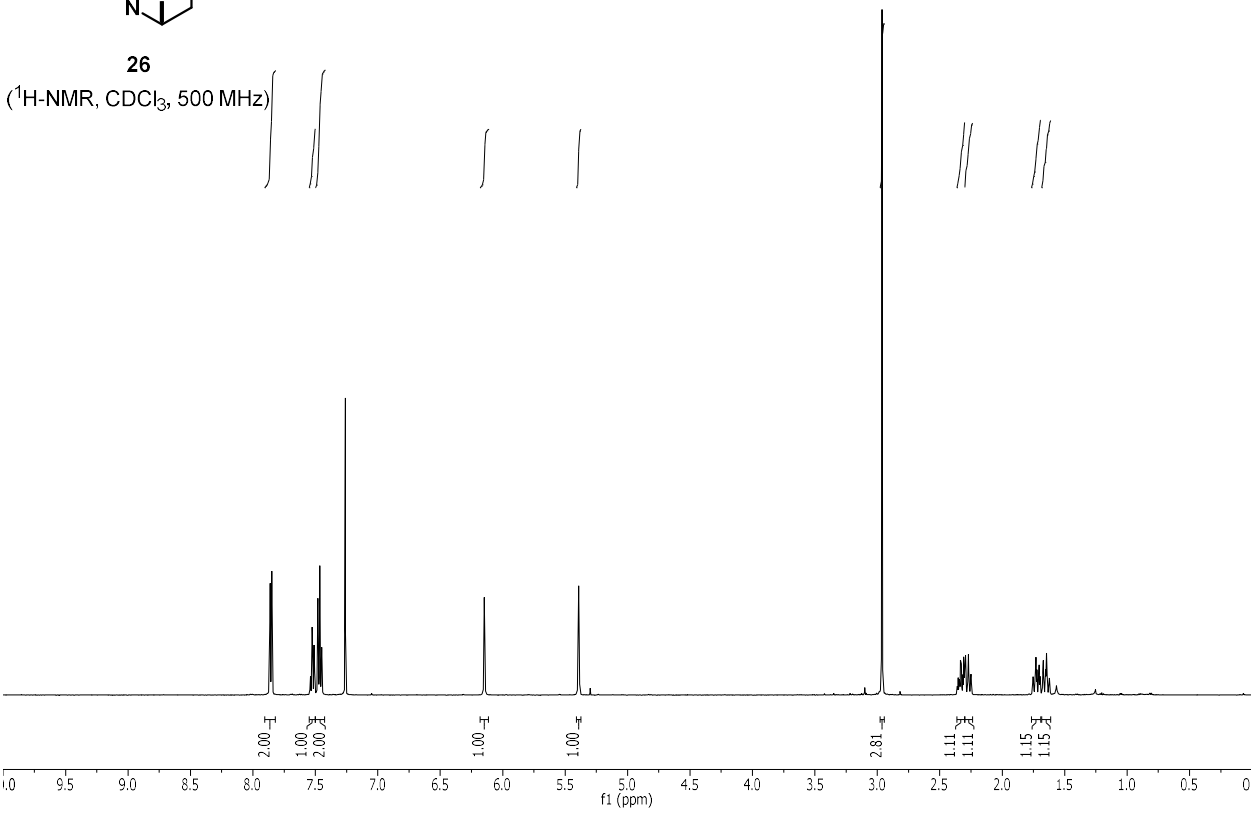

Ph
X
25
(1H-NMR, CDCl3, 500 MHz)
2.07
3.10
1.00
1.00
0.99
3.04
2.03
2.05
f1 (ppm)

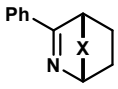

Ph
X
25
(13C-NMR, CDCl3, 126 MHz)
f1 (ppm)



26

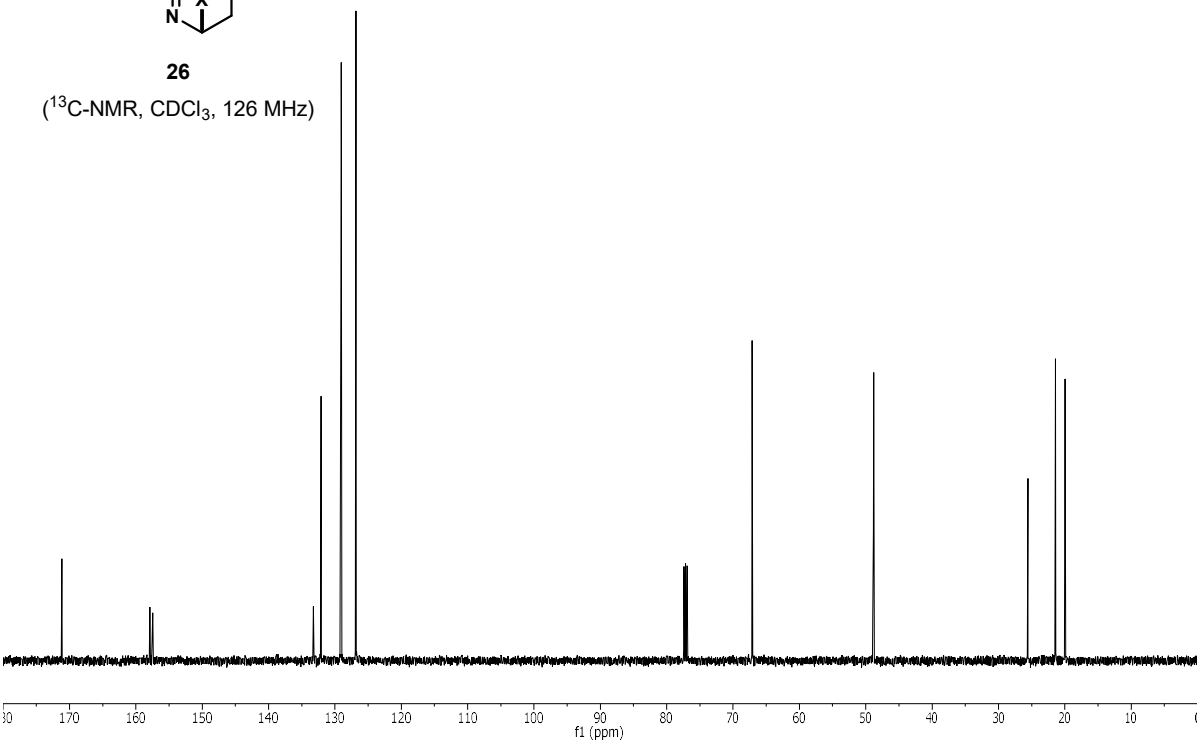
(^{1}H-NMR, $CDCl_3$, 500 MHz)

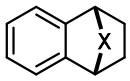




26

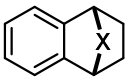
(^{13}C-NMR, $CDCl_3$, 126 MHz)





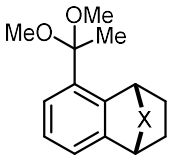
28

(^{1}H NMR, $CDCl_3$, 500 MHz)

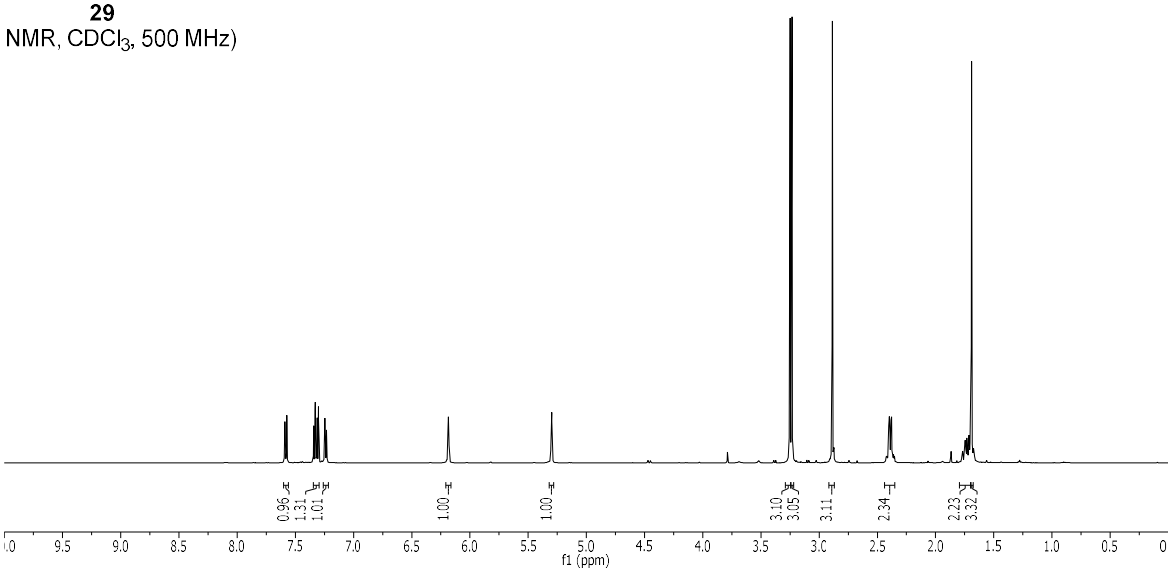


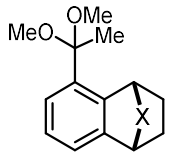
28

(^{13}C NMR, $CDCl_3$, 126 MHz)

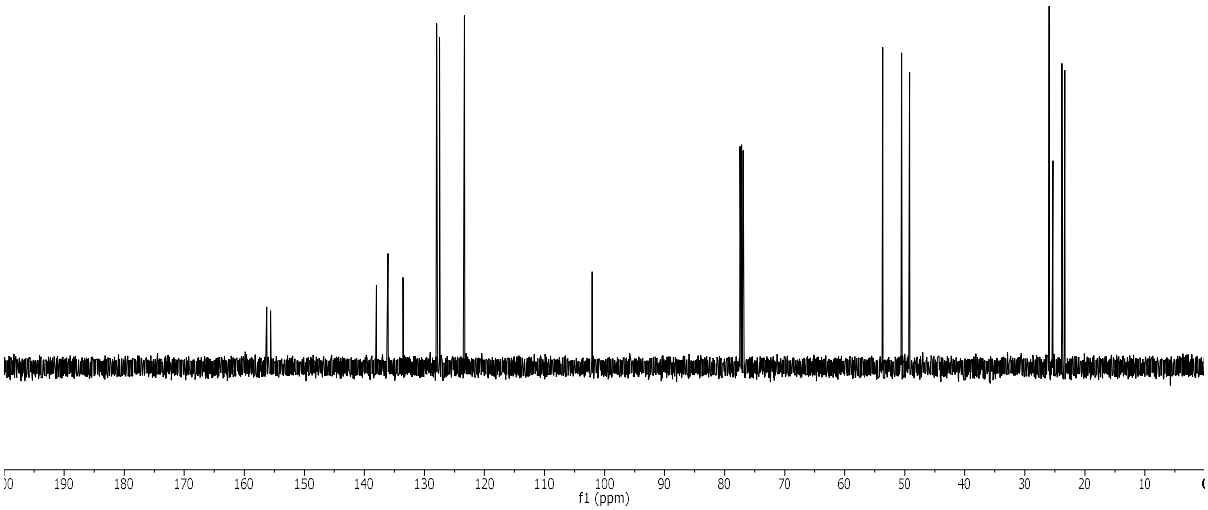


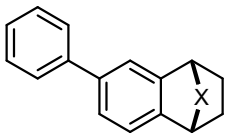
29
(^{1}H NMR, $CDCl_3$, 500 MHz)



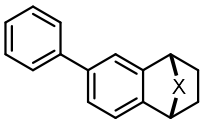


29
(^{13}C NMR, $CDCl_3$, 126 MHz)

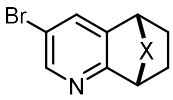




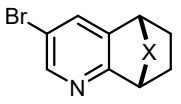
30
(^{1}H NMR, $CDCl_3$, 500 MHz)



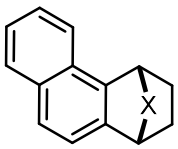
30
(^{13}C NMR, $CDCl_3$, 126 MHz)



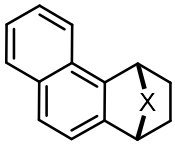
31
(^{1}H NMR, $CDCl_3$, 500 MHz)



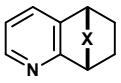
31
(^{13}C NMR, $CDCl_3$, 126 MHz)



32
(^{1}H NMR, $CDCl_3$, 500 MHz)

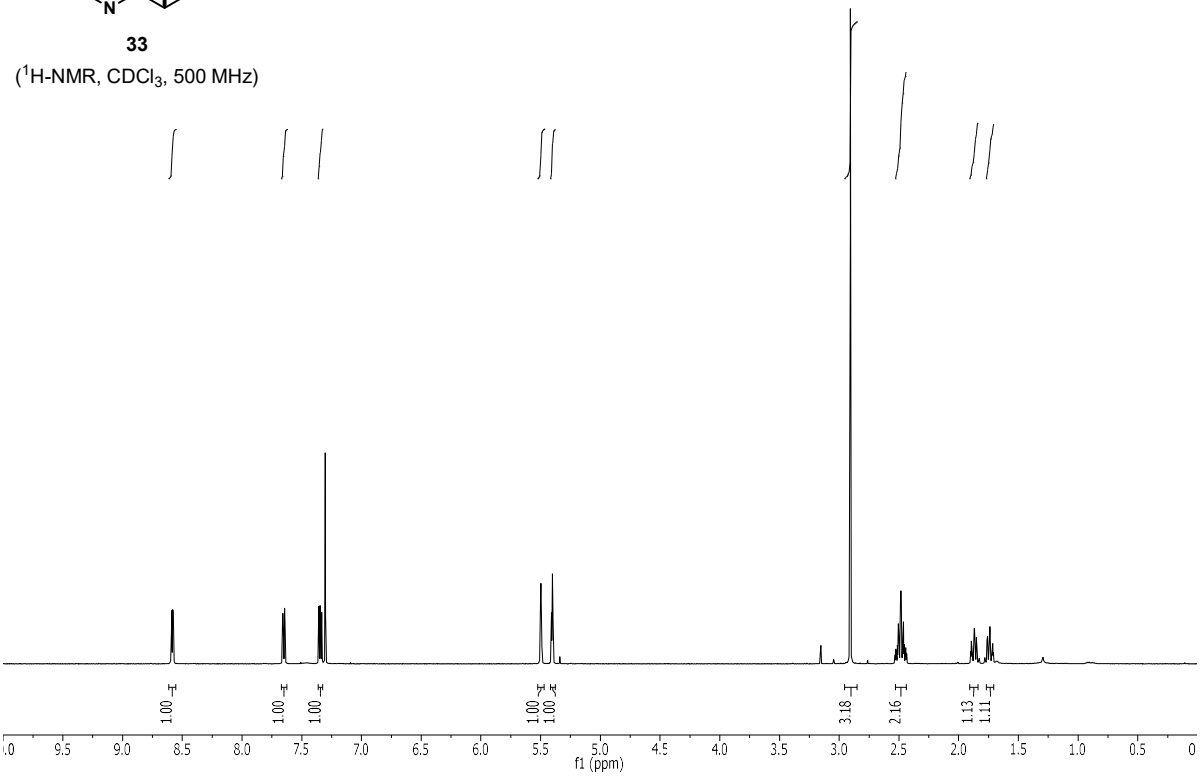


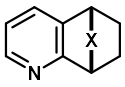
32
(^{13}C NMR, $CDCl_3$, 126 MHz)



33

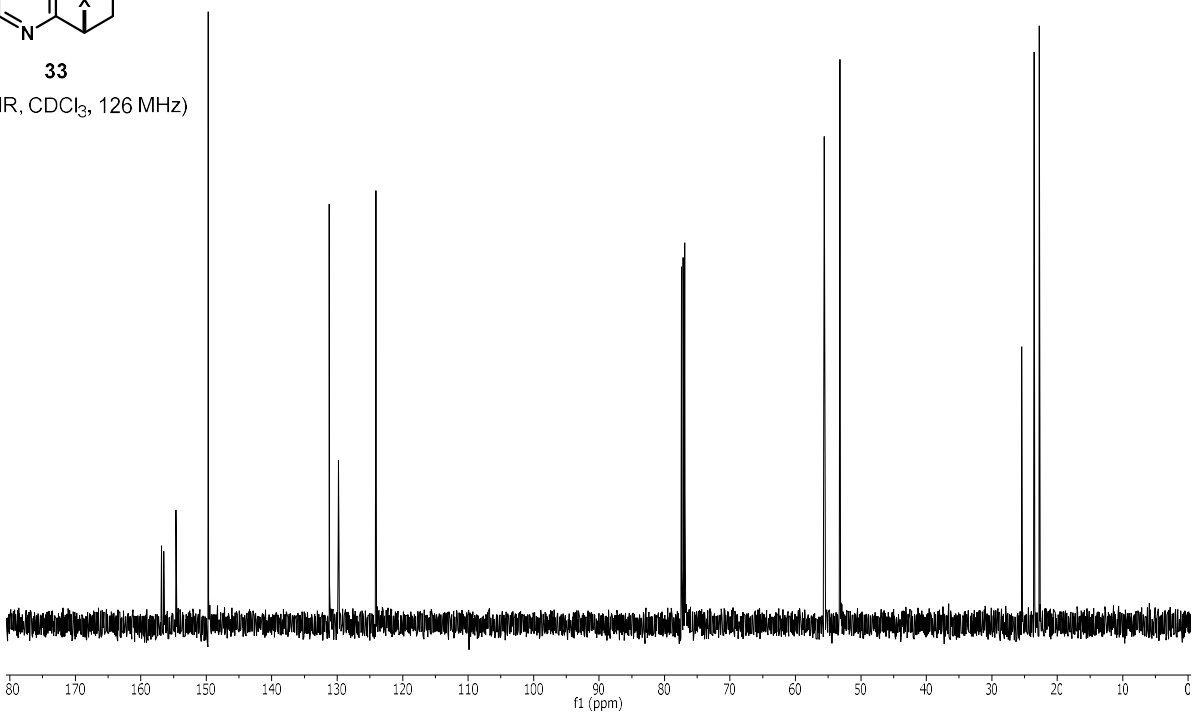
(^{1}H-NMR, $CDCl_3$, 500 MHz)

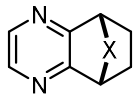




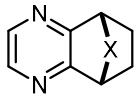
33

(^{13}C-NMR, $CDCl_3$, 126 MHz)

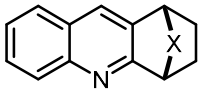




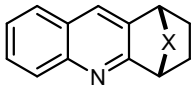
34
(^{1}H NMR, $CDCl_3$, 500 MHz)



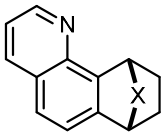
34
(^{13}C NMR, $CDCl_3$, 126 MHz)



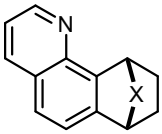
35
(^{1}H NMR, $CDCl_3$, 500 MHz)



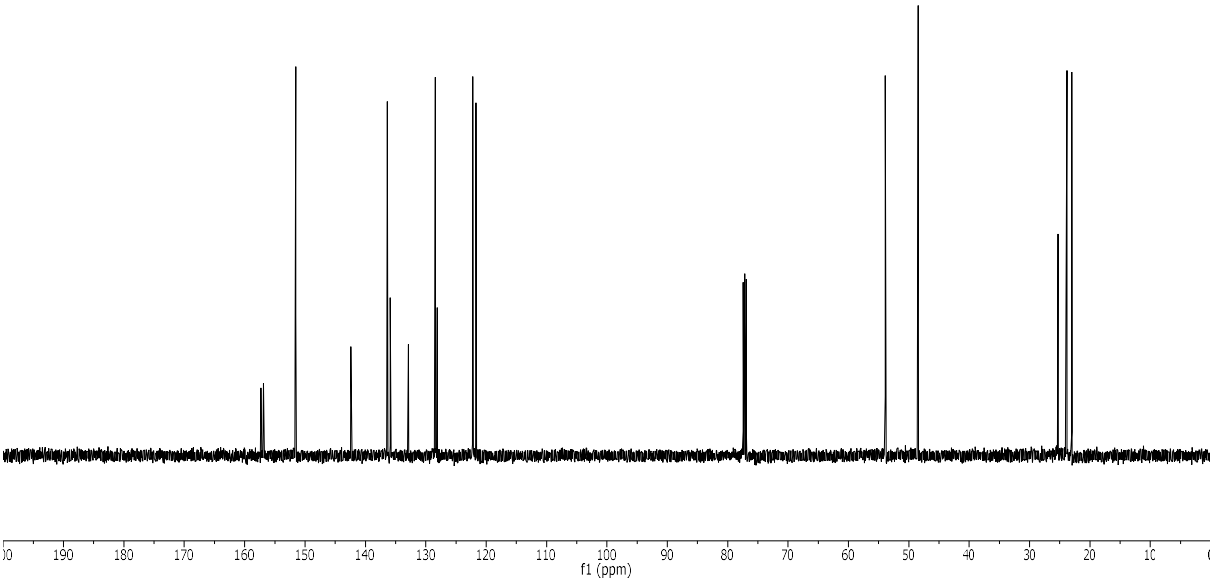
35
(^{13}C NMR, $CDCl_3$, 126 MHz)

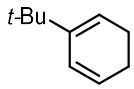


36
(^{1}H NMR, $CDCl_3$, 500 MHz)



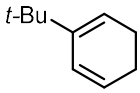
36
(^{13}C NMR, $CDCl_3$, 126 MHz)





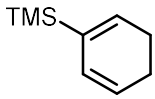
38

(^{1}H NMR, $CDCl_3$, 500 MHz)



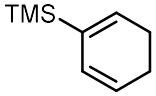
38

(^{13}C NMR, $CDCl_3$, 126 MHz)



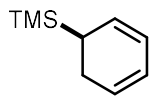
39

(^{1}H NMR, $CDCl_3$, 500 MHz)



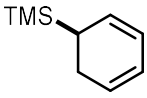
38

(^{13}C NMR, $CDCl_3$, 126 MHz)



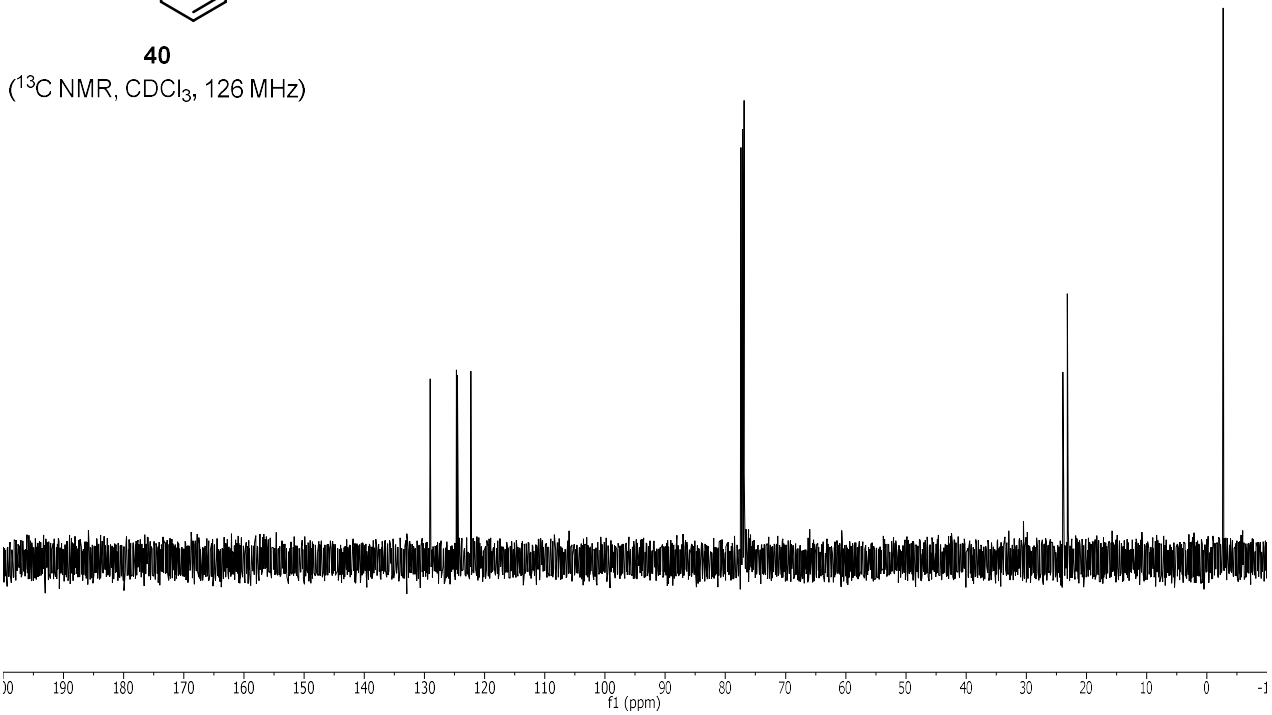
40

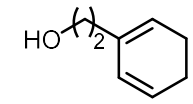
(^{1}H NMR, $CDCl_3$, 500 MHz)



40

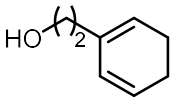
(^{13}C NMR, $CDCl_3$, 126 MHz)





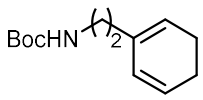
41

(^{1}H NMR, $CDCl_3$, 500 MHz)



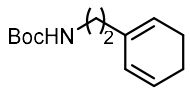
41

(^{13}C NMR, $CDCl_3$, 126 MHz)



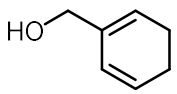
42

(^{1}H NMR, $CDCl_3$, 500 MHz)



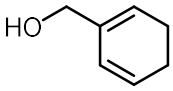
42

(^{13}C NMR, $CDCl_3$, 126 MHz)



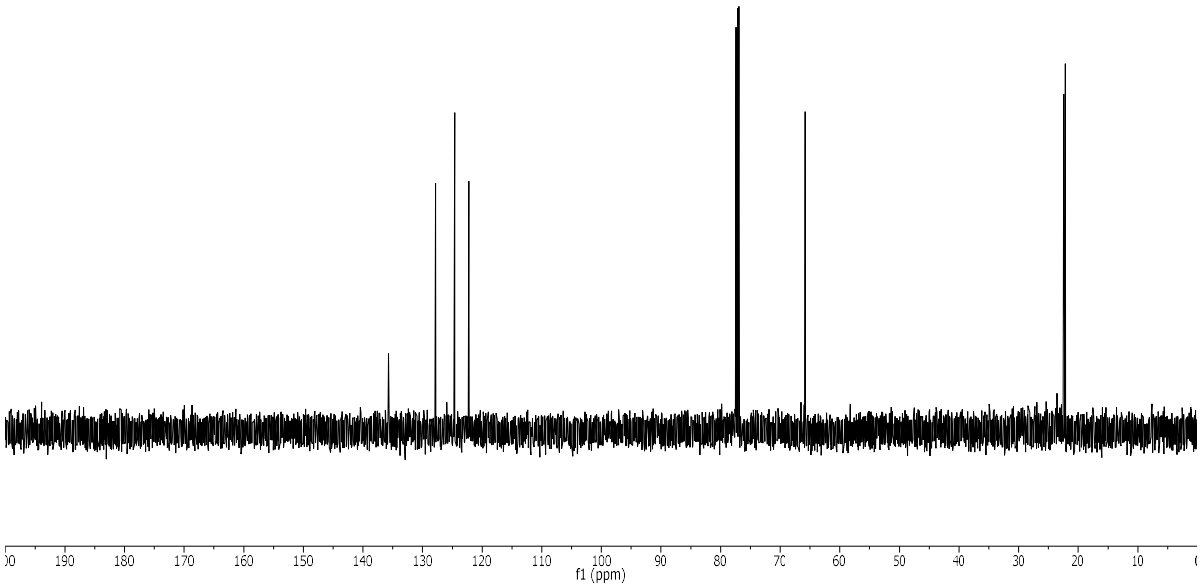
43

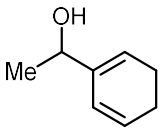
(^{1}H NMR, $CDCl_3$, 500 MHz)



43

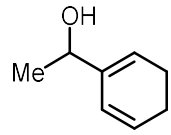
(^{13}C NMR, $CDCl_3$, 126 MHz)





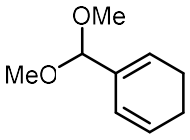
44

(^{1}H NMR, $CDCl_3$, 500 MHz)



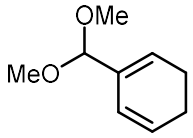
44

(^{13}C NMR, $CDCl_3$, 126 MHz)



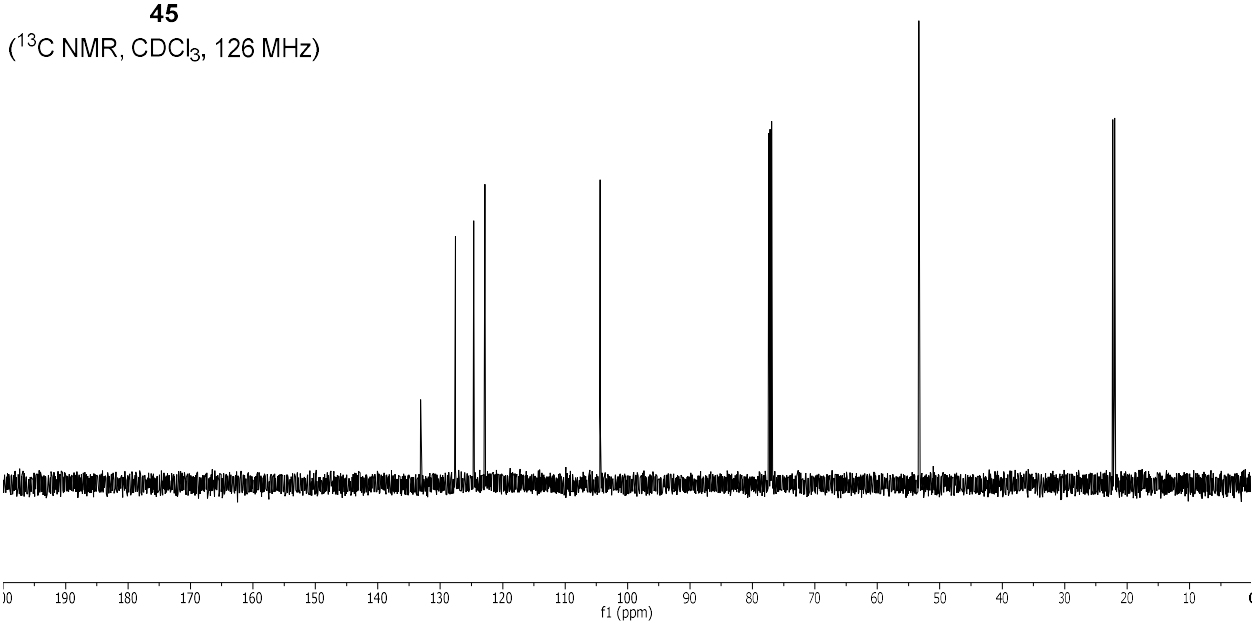
45

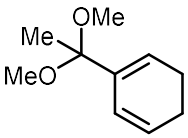
(^{1}H NMR, $CDCl_3$, 500 MHz)



45

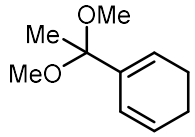
(^{13}C NMR, $CDCl_3$, 126 MHz)





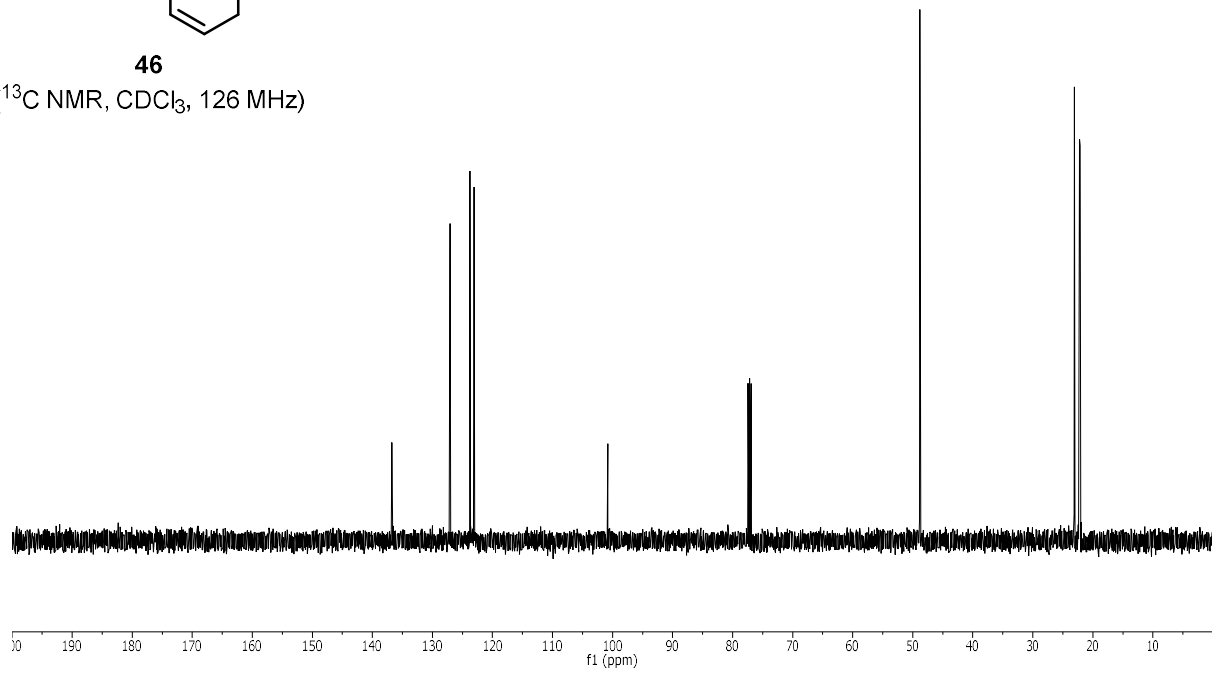
46

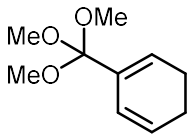
(^{1}H NMR, $CDCl_3$, 500 MHz)



46

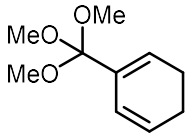
(^{13}C NMR, $CDCl_3$, 126 MHz)





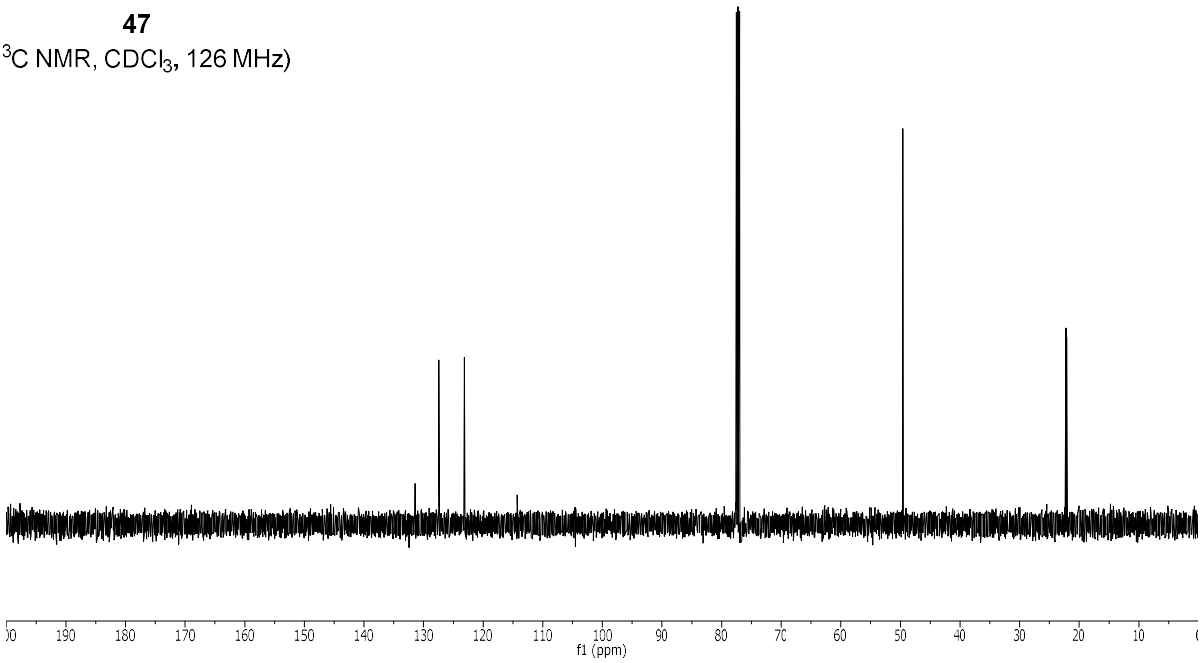
47

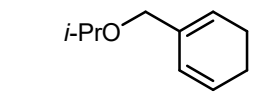
(^{1}H NMR, $CDCl_3$, 500 MHz)



47

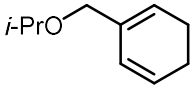
(^{13}C NMR, $CDCl_3$, 126 MHz)





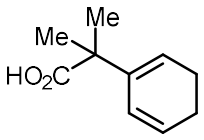
48

(^{1}H NMR, $CDCl_3$, 500 MHz)



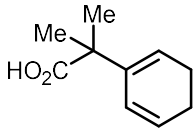
48

(^{13}C NMR, $CDCl_3$, 126 MHz)



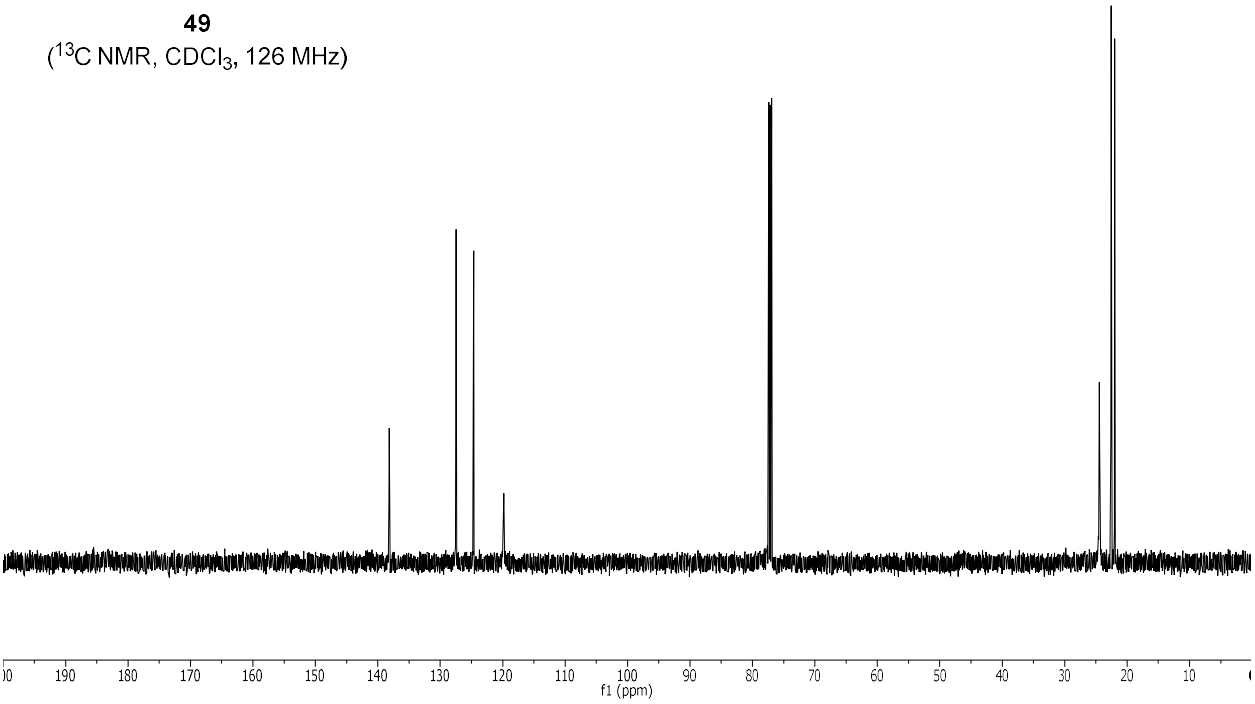
49

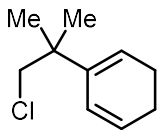
(^{1}H NMR, $CDCl_3$, 500 MHz)



49

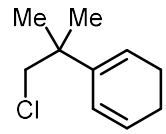
(^{13}C NMR, $CDCl_3$, 126 MHz)





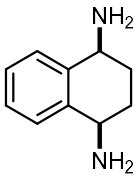
50

(^{1}H NMR, $CDCl_3$, 500 MHz)



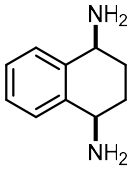
50

(^{13}C NMR, $CDCl_3$, 126 MHz)



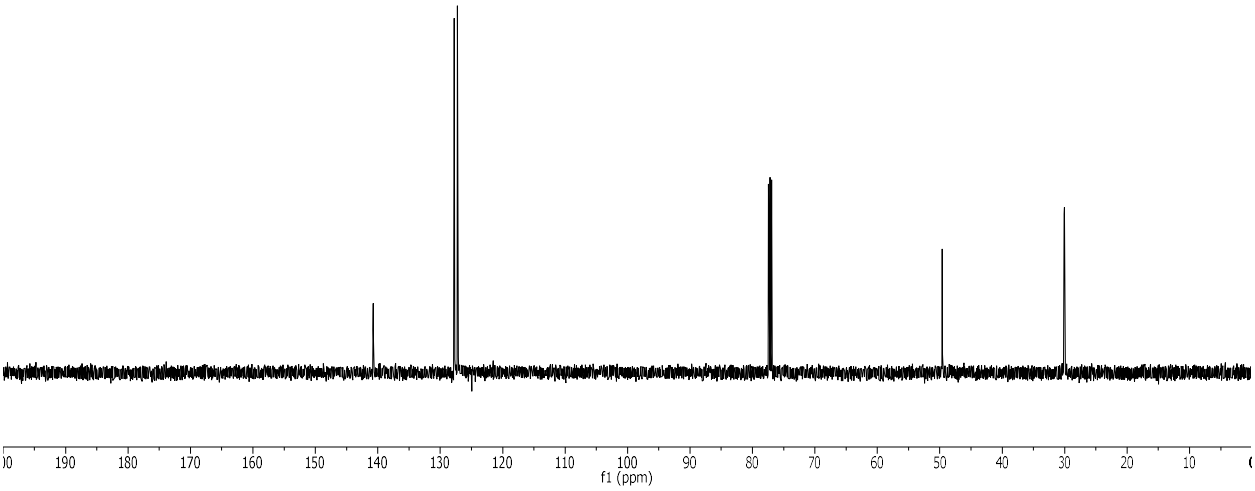
52

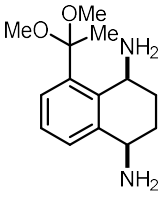
(^{1}H NMR, $CDCl_3$, 500 MHz)



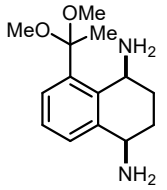
52

(^{13}C NMR, $CDCl_3$, 126 MHz)

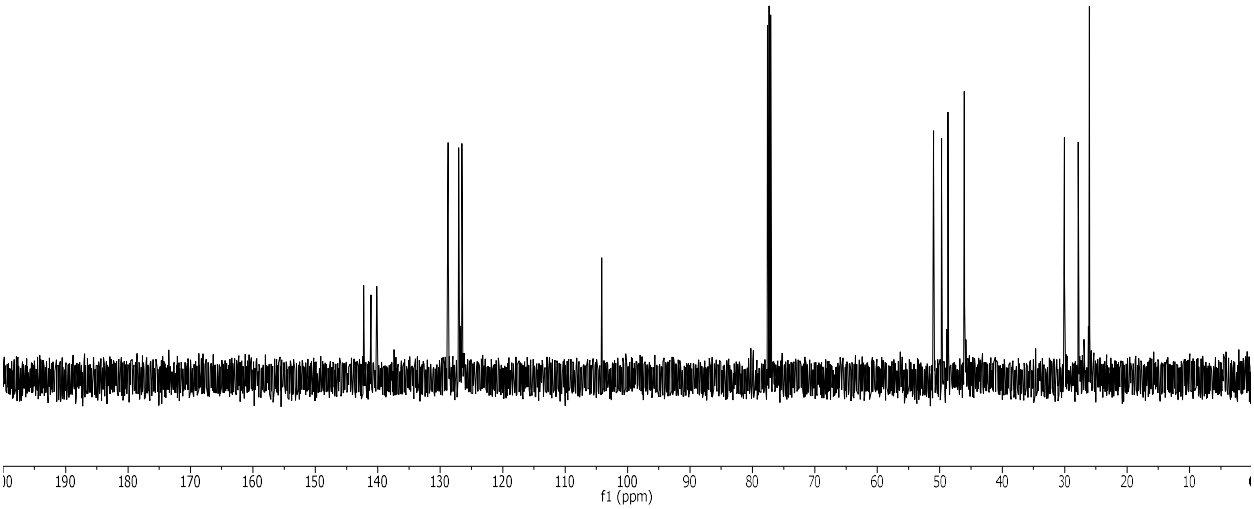


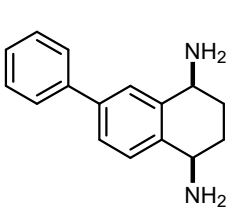


53
(^{1}H NMR, $CDCl_3$, 500 MHz)

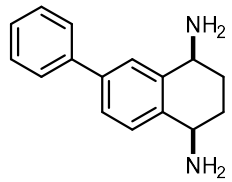


53
(^{13}C NMR, $CDCl_3$, 126 MHz)

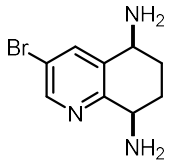




54
(^{1}H NMR, $CDCl_3$, 500 MHz)

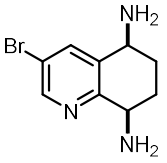


54
(^{13}C NMR, $CDCl_3$, 126 MHz)



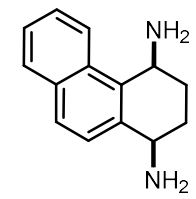
55

(^{1}H NMR, $CDCl_3$, 500 MHz)



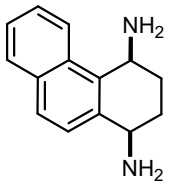
55

(^{13}C NMR, $CDCl_3$, 126 MHz)



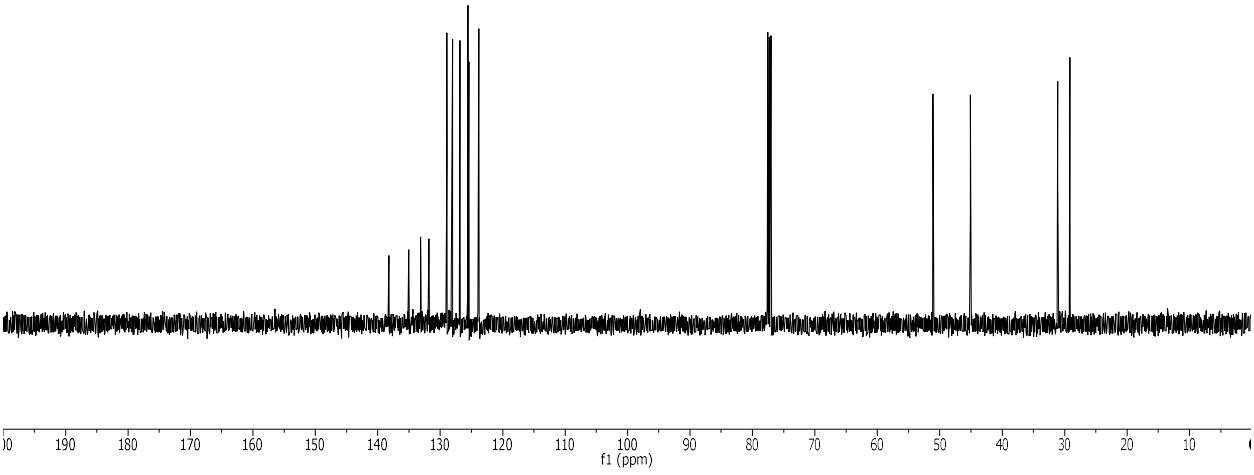
56

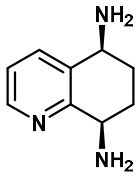
(^{1}H NMR, $CDCl_3$, 500 MHz)



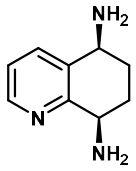
56

(^{13}C NMR, $CDCl_3$, 126 MHz)

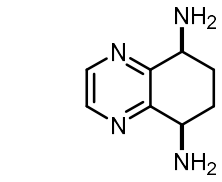




57
(^{1}H-NMR, $CDCl_3$, 500 MHz)

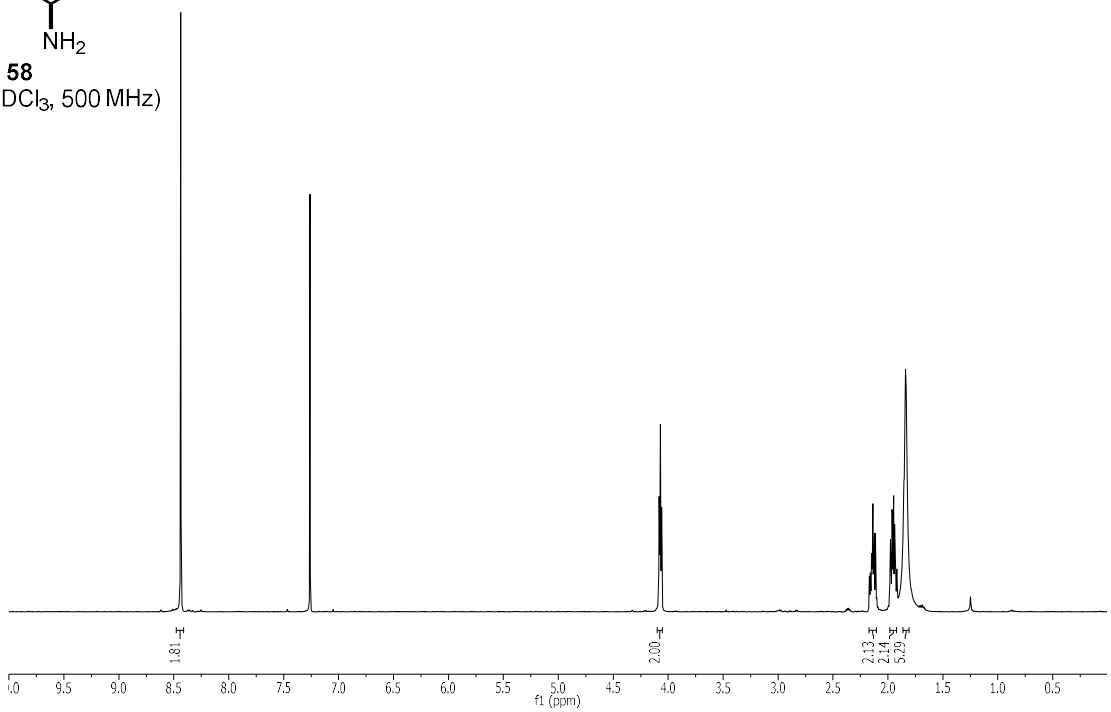


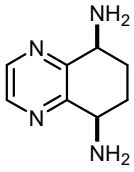
57
(^{13}C-NMR, $CDCl_3$, 126 MHz)



58

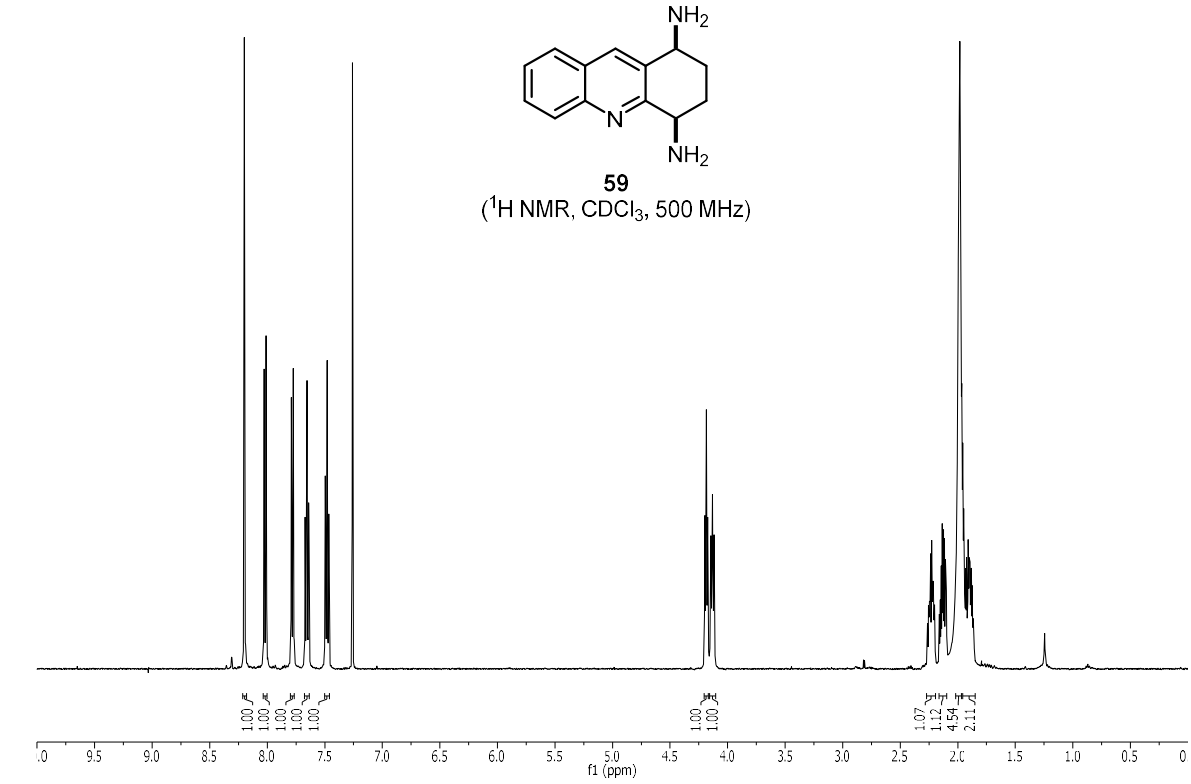
(^{1}H NMR, $CDCl_3$, 500 MHz)



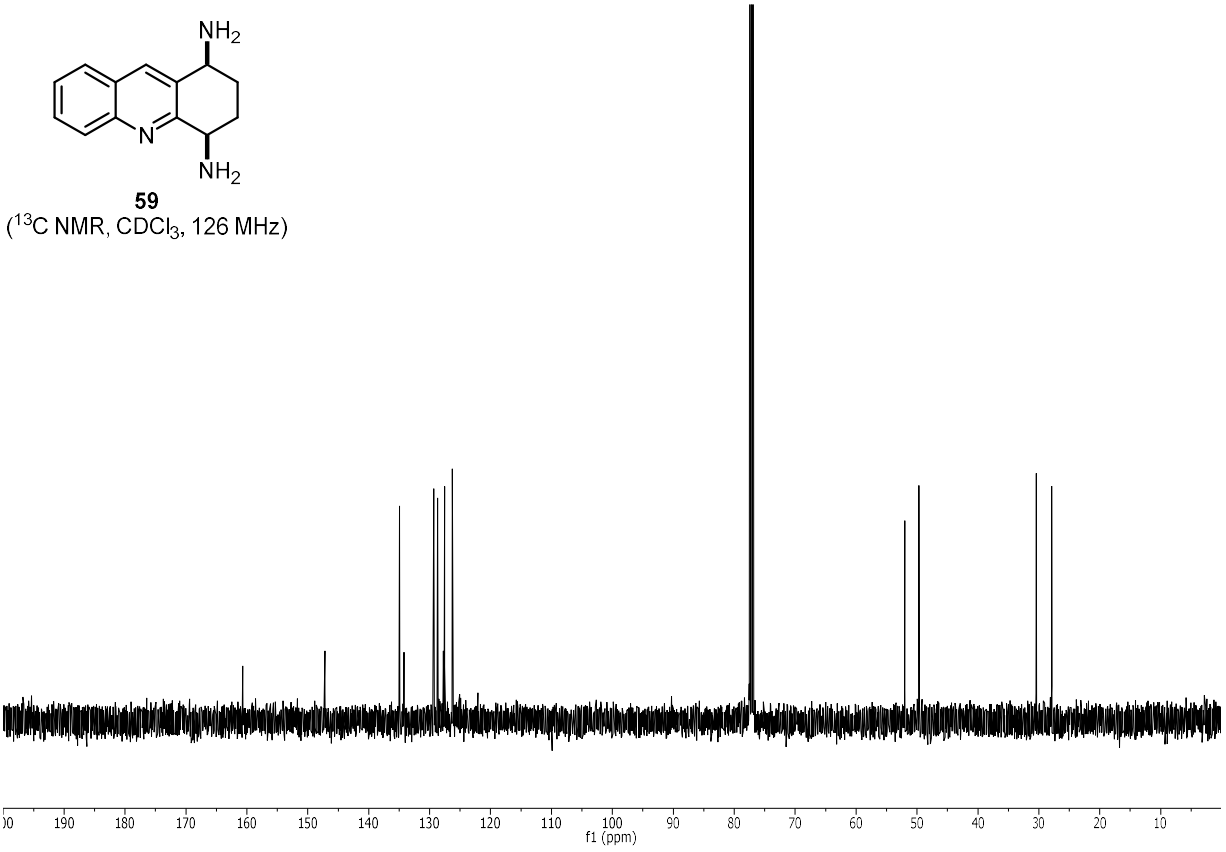


58

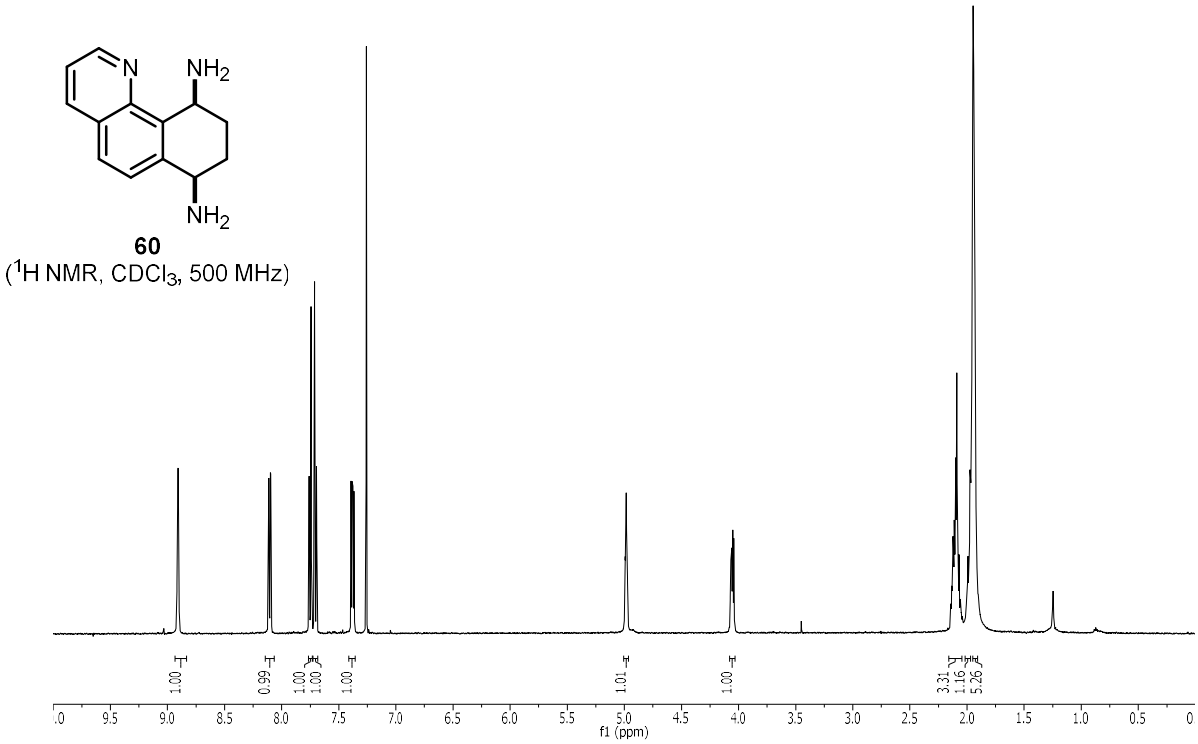
(^{13}C NMR, $CDCl_3$, 126 MHz)



59
(^{1}H NMR, $CDCl_3$, 500 MHz)

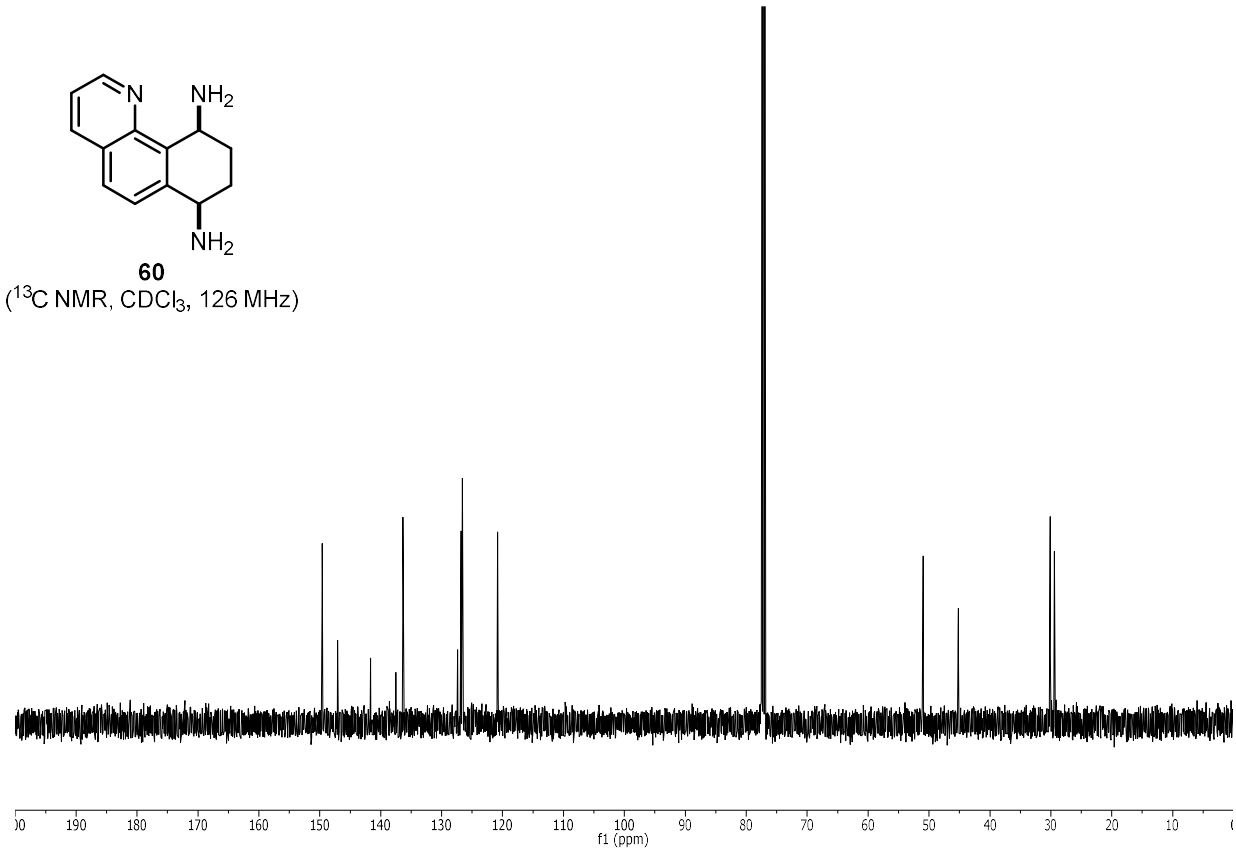


59
(^{13}C NMR, $CDCl_3$, 126 MHz)



60

(^{1}H NMR, $CDCl_3$, 500 MHz)



60

(^{13}C NMR, $CDCl_3$, 126 MHz)